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(54) **TETRAHYDROISOQUINOLIN-1-ONE
DERIVATIVE OR SALT THEREOF**

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417/12** (2013.01); **C07D 453/02** (2013.01);
C07D 471/04 (2013.01)

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(58) **Field of Classification Search**
CPC A61K 31/435; A61K 31/439
See application file for complete search history.

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(51) **Int. Cl.**

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A61K 31/445	(2006.01)
C07D 401/12	(2006.01)
C07D 217/26	(2006.01)
C07D 401/04	(2006.01)
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C07D 401/14	(2006.01)
C07D 405/04	(2006.01)
C07D 405/06	(2006.01)
C07D 405/14	(2006.01)
C07D 409/12	(2006.01)
C07D 413/12	(2006.01)
C07D 417/12	(2006.01)
C07D 453/02	(2006.01)
C07D 471/04	(2006.01)

(52) **U.S. Cl.**

CPC **C07D 401/12** (2013.01); **A61K 31/435**
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C07D 401/04 (2013.01); **C07D 401/06**
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405/04** (2013.01); **C07D 405/06** (2013.01);
C07D 405/14 (2013.01); **C07D 409/12**

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(57) **ABSTRACT**

To provide a pharmaceutical, in particular a compound which
can be used as a therapeutic agent for irritable bowel syn-
drome (IBS). It was found that a tetrahydroisoquinolin-1-one
derivative having an amide group at the 4-position or a phar-
maceutically acceptable salt thereof has an excellent bomb-
besin 2 (BB2) receptor antagonistic action. It is also found that
the tetrahydroisoquinolin-1-one derivative is highly effective
on bowel movement disorders. From the above, the tetrahy-
droisoquinolin-1-one derivative of the present invention is
useful as a therapeutic agent for diseases associated with a
BB2 receptor, in particular IBS.

7 Claims, No Drawings

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TETRAHYDROISOQUINOLIN-1-ONE DERIVATIVE OR SALT THEREOF

This application is a Divisional of U.S. patent application Ser. No. 12/600,894, filed Nov. 19, 2009, which is the U.S. National Phase of PCT/JP2008/059621, filed Mar. 26, 2008, which claims priority from Japanese Patent Application No. P2007-140097, filed May 28, 2007, all of which are incorporated herein by reference in entirety.

TECHNICAL FIELD

The present invention relates to a pharmaceutical, in particular, a tetrahydroisoquinolin-1-one derivative or a salt thereof, which is useful as a therapeutic agent for irritable bowel syndrome.

BACKGROUND ART

Irritable bowel syndrome (IBS) is a syndrome which causes chronic symptoms such as abdominal pain, bloating, and the like, bowel movement disorders such as diarrhea, constipation, and the like, defecation trouble, defecation straining, and the like. It is caused by functional abnormality of the lower digestive tract, mainly the large intestine, despite the absence of organic disorders such as inflammation, tumors, and the like, and is classified based on the conditions of stool into diarrhea-predominant, constipation-predominant, and alternating IBS which alternately repeats diarrhea and constipation. IBS is a disease which has a relatively high frequency occupying from 20 to 50% of bowel disease patients who consult outpatient cares, which is predominant in females with a male to female ratio of 1:2 regardless of race, and which has a high prevalence rate in the younger generation. Since mental stress correlates strongly with the state of the disease, it is regarded as a representative stress-related somatic disease and it is said that the stress management is important for the improvement of symptoms. Actually, it is known that abnormal motility of gastrointestinal tract is significantly accelerated and the symptoms are aggravated when emotional stress is applied to IBS patients. In addition, since the symptoms continue, a vicious circle is likely to form in which increased patient anxiety further aggravates the symptoms.

As the drug therapy of IBS, an anticholinergic is used for abdominal pain, and a tricyclic antidepressant for the improvement of pain threshold value reduction in the digestive tracts, and for the improvement of abnormal bowel motility, a stegnotic, a drug for controlling intestinal function, and the like in the case of diarrhea, and a saline cathartic and the like in the case of constipation, however these are merely symptomatic therapies and their effects are not clear. As an agent from which effects can be expected for both diarrhea and constipation, there is polycarbophil calcium, which regulates the hardness of feces by gelating in the intestines, however it exerts very limited effects because not only there is a bloating at the initial stage of its administration but also it requires time to exhibit the effects. Anxiolytics and antidepressants are used when anxiety and tension are considerably increased due to stress, however they are administered at a dose lower than the dose in the psychiatric field, so that there are cases in which the mental symptoms are not improved or cases in which these are improved but they do not exhibit any effects on the bowel movement disorder. Generally, among the symptoms of IBS, anxiolytics are effective for diarrhea and abdominal pain in some cases, but they have a tendency to exhibit little effect on constipation.

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There are a 5-HT₃ receptor antagonist alosetron and a 5-HT₄ receptor agonist tegaserod as the agents, which have been drawing attention in recent years, and they are used in the diarrhea-predominant and the constipation-predominant, respectively. These agents improve the bowel movement by regulating the movement of intestines, and exhibit an effect quickly. However, though alosetron shows a relatively high improving rate of from 40 to 60% for abdominal symptoms and diarrhea, constipation occurs in 30 to 35% of the patients and it causes ischemic colitis (including mortal cases) as a serious side effect, so that its use is limited (Non-Patent Document 1). In addition, it cannot be said that the effect of tegaserod on the constipation-predominant is sufficient, and there is a possibility of causing tachyphylaxis (a phenomenon in which resistance is generated when a drug is repeatedly administered within a short period of time).

Apropos, when the living body receives a stress, it generates a hypothalamic-pituitary-adrenal system (HPA system) reaction, in which an adrenocorticotrophic hormone (ACTH) is released through the secretion of a stress-related substance from the hypothalamus and a subsequent action upon the anterior hypophysis, and the ACTH released into the blood secretes corticosterone from the adrenal cortex, and thereby shows various stress responses such as increase in the blood pressure and the like. As the stress-related substance, corticotropin releasing hormone (CRH), bombesin (BB)/gastrin releasing peptide (GRP), vasopressin, neuropeptide Y, substance P, neurotensin, and the like are known. Secretion of these substances from the hypothalamus is accelerated when a stress is applied to an animal. Particularly regarding the CRH, it has been reported that it reinforces ACTH release and large bowel movement when administered to IBS patients (Non-Patent Document 2).

The bombesin/GRP as one of the stress-related substances is a brain-gut peptide and expresses various physiological actions via bombesin receptors. The bombesin receptor is classified into 3 subtypes of BB1, BB2 and BB3/BRS3 (bombesin receptor subtype-3), and as intrinsic ligands of mammals for the BB1 and BB2 receptors, neuromedin B and GRP have been identified respectively. It has been reported that the GRP and BB2 receptors are present ubiquitously in the brain, the digestive tracts, and the like, but GRP is markedly increased in the amygdala and hypothalamus when stress is applied to an animal (Non-Patent Document 3). In addition, it has been reported also that a BB2 receptor antagonist inhibits the increase in ACTH when administered into the cerebral ventricle in a restraint stress-added rat (Non-Patent Document 4).

As the role of the GRP/BB2 receptor in the digestive tract functions, it has been reported that it enhances the contraction in isolated human and rabbit ileum longitudinal muscle specimens (Non-Patent Documents 5 and 6), and enhances the water secretion in guinea pigs with the coexistence of a vasoactive intestinal peptide (VIP) (Non-Patent Document 7). In addition, it has been reported that BB2 receptor antagonists including RC-3095 that is a peptidic BB2 receptor antagonist, is effective for an abnormal bowel motility in a stress-induced defecation model. It has also been reported that, using an abdominal muscle contraction reaction as the index, RC-3095 is effective for an abdominal symptom in an abdominal pain model induced by large intestinal distension. Accordingly the BB2 receptor antagonist shows excellent efficacy on both the abdominal symptom and abnormal bowel motility (Patent Document 1).

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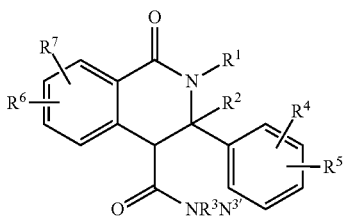
As shown above, the BB2 receptor antagonist is expected to be a therapeutic agent for IBS, showing excellent efficacy on both the abdominal symptom and abnormal bowel motility.

Furthermore, since the bombesin/GRP also has a function as a cell growth factor and the expression of the GRP/BB2 receptor is increased in various cancer cells of lung cancer, prostate cancer, and the like, the efficacy of RC-3095 has been reported in a large number of antitumor tests (Non-Patent Documents 8 to 10). From this viewpoint, the BB2 receptor antagonist can also be expected to be effective against various cancers.

The tetrahydroisoquinolin-1-one derivative has been reported in Patent Documents 2 to 4.

Patent Document 2 describes that a 3,4-dihydroisoquinolin-1-one derivative represented by the following formula (A) has a caspase activating action and an apoptosis inducing action, and is effective for cancers, autoimmune diseases, rheumatoid arthritis, inflammatory bowel syndrome, psoriasis, and the like. However, there is no description of its antagonistic action on a bombesin type 2 receptor or of its efficacy regarding IBS.

[Chem. 1]

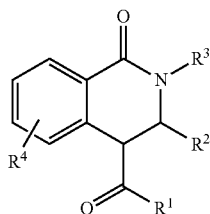


(for the symbols in the formula, refer to the publication)

Patent Document 3 describes that a tetrahydroisoquinolin-1-one derivative represented by the following formula (B) is a ligand of an HDM2 protein, has an apoptosis inducing activity and a proliferation inhibitory activity, and is effective against cancers.

However, there is no description of its antagonistic action on a bombesin type 2 receptor or of its efficacy regarding IBS.

[Chem. 2]



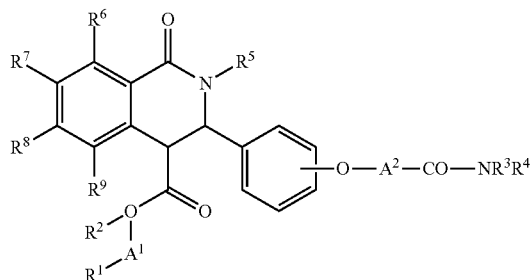
(for the symbols in the formula, refer to the publication)

Patent Document 4 describes that a tetrahydroisoquinolin-1-one derivative represented by the following formula (C) is a neurotensin-2 (NT-2) receptor antagonist and is effective against pain. However, for R5 corresponding to R1 of the present invention, there is no description on the R1 group of the present invention. In addition, there is no description of its antagonistic action on a bombesin type 2 receptor or of its efficacy regarding IBS.

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[Chem. 3]

(C)



(wherein R5 means (C1-C8) alkyl which is optionally substituted with a group selected from trifluoromethyl, halogen, saturated or partially unsaturated (C3-C8)cycloalkyl, and (C6-C10) aryl. For the other symbols, refer to the publication.)

The compounds described in the following Tables 1 to 11 below are reported as Catalog Compounds. However, there is no description of the antagonistic action on a bombesin type 2 receptor and the efficacy for IBS, of these compounds. Further, in the following Tables, the abbreviations below are used. Me: Methyl, Et: Ethyl, iPr: Isopropyl, nBu: Normal Butyl, Ph: Phenyl.

TABLE 1

CAS Registry No.	R ^a R ^b N—
931939-66-1	
931315-65-0	
902607-43-6	Me ₂ N—
902450-09-3	Ph—(CH ₂) ₂ —NH—
891914-00-4	PhCH ₂ —NH—
891913-84-1	

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TABLE 1-continued

CAS Registry No.	R ^a R ^b N—
891913-76-1	
891913-68-1	
891913-28-3	
891913-04-5	
891912-88-2	
891912-80-4	

TABLE 2

891912-64-4	
891912-56-4	
891912-48-4	
891912-40-6	

6

TABLE 2-continued

891912-16-6	
891912-08-6	
891912-00-8	
891911-84-5	
891911-60-7	
891911-52-7	
891911-44-7	
891911-36-7	

TABLE 3

891911-29-8	
891911-22-1	
891911-07-2	
891910-93-3	

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TABLE 3-continued

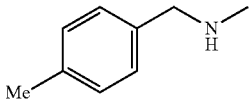
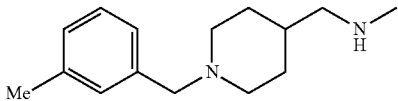
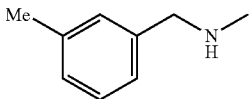
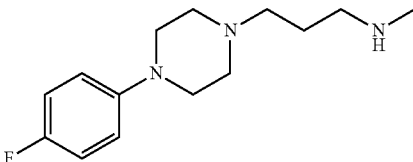
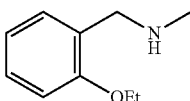
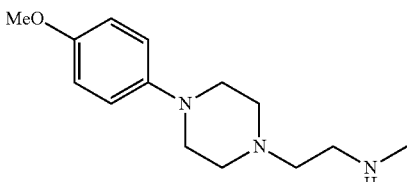
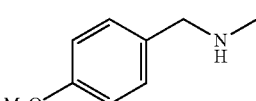
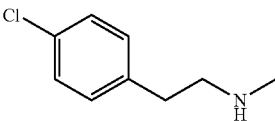
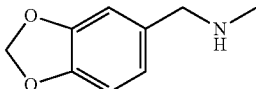
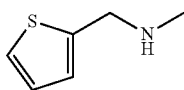
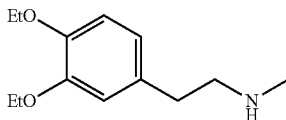
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891910-72-8	
891910-65-9	
891910-58-0	
891910-23-9	
891910-07-9	
891909-99-2	
891909-91-4	$\text{EtO}-(\text{CH}_2)_3-\text{NH}-$
891909-83-4	

TABLE 4

891909-75-4	
891909-67-4	
891909-59-4	$\text{iPrO}-(\text{CH}_2)_3-\text{NH}-$
891909-51-6	

8

TABLE 4-continued

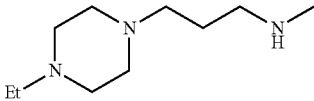
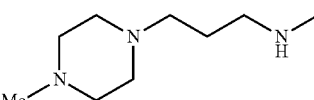
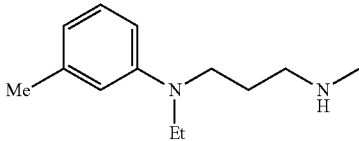
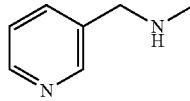
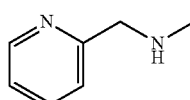
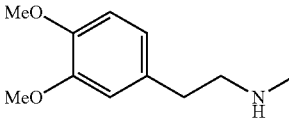
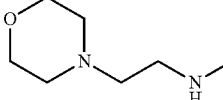
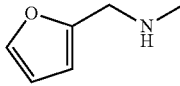
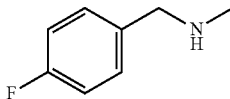
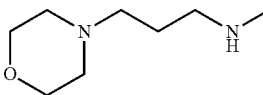
891909-27-6	$\text{PhN}(\text{Et})-(\text{CH}_2)_3-\text{NH}-$
5 891909-11-8	
10 891909-03-8	
15 891908-95-5	
20 891908-55-7	$\text{Et}_2\text{N}-$
25 891907-99-6	
30 891907-91-8	
35 891907-83-8	
40 891907-75-8	
45 891907-43-0	$\text{MeO}-(\text{CH}_2)_3-\text{NH}-$
891907-35-0	$\text{nBuNH}-$
891907-27-0	$\text{iPrNH}-$
50 891907-19-0	
55 891907-11-2	$\text{MeO}-(\text{CH}_2)_2-\text{NH}-$

TABLE 5

891907-03-2	
60 891906-95-9	
65	

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TABLE 5-continued

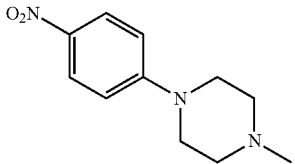
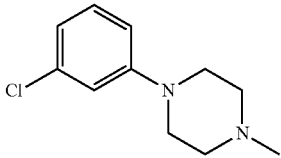
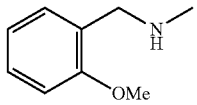
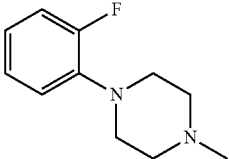
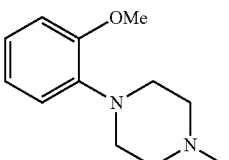
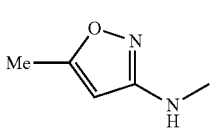
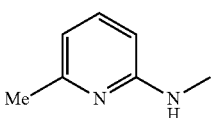
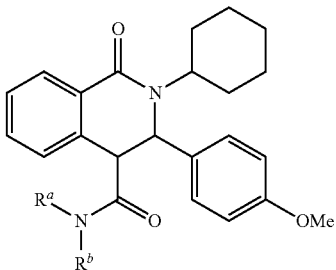
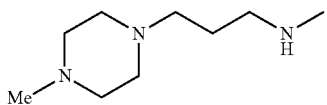
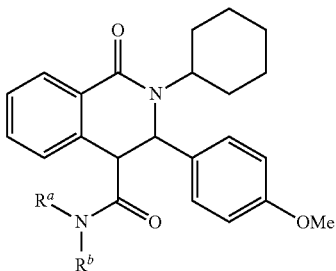
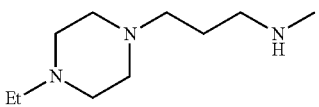
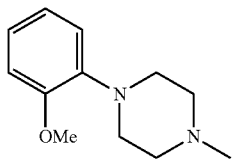
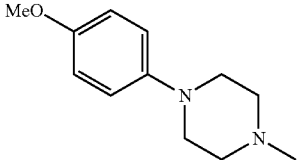
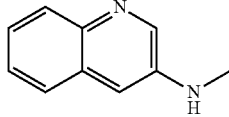
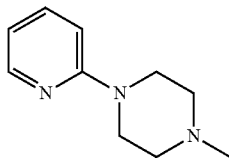
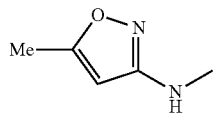
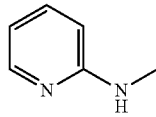
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891906-79-9	
891906-71-1	
891906-55-1	
891906-39-1	
891905-75-2	
891904-87-3	

TABLE 6

	
CAS Registry No.	$R^a R^b N-$
685520-62-1	

10

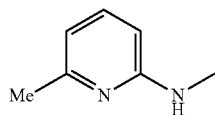
TABLE 6-continued

5	
10	
15	CAS Registry No. $R^a R^b N-$
685520-61-0	
20	
442858-62-0	EtO_2C-CH_2-NH-
442858-61-9	
25	
30	
442858-27-7	$MeO_2C-(CH_3)_2-NH-$
442858-05-1	MeO_2C-CH_2-NH-
442858-04-0	
35	
40	
442857-76-3	
45	
442857-73-0	
50	
442856-86-2	
55	
442856-85-1	
60	
65	442856-80-6 Et_2N-

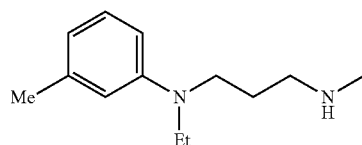
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TABLE 7

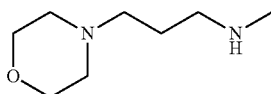
442856-71-5



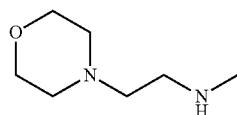
442856-34-0



442856-31-7



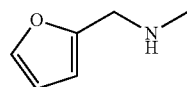
442856-30-6



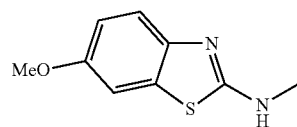
442856-29-3

iPrNH—

442856-28-2



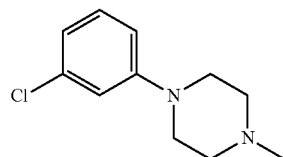
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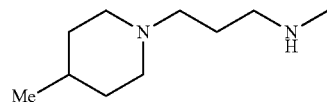
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PhN(Et)—(CH₂)₃—NH—

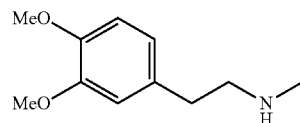
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442854-93-5



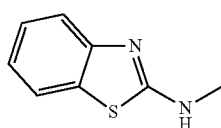
442854-92-4



442854-57-1

MeO—(CH₂)₂—NH—

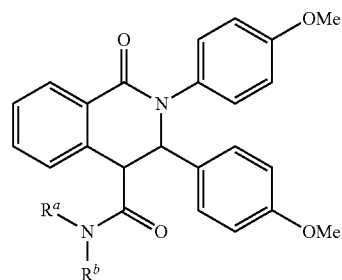
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12

TABLE 8

5



10

CAS Registry No.

685520-63-2

20

442859-46-3

25

442859-42-9

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442859-40-7

35

442859-39-4

40

442859-38-3

45

442859-36-1

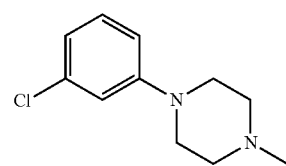
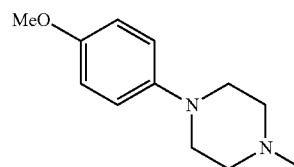
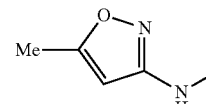
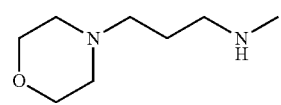
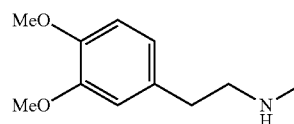
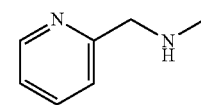
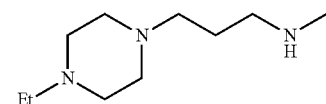
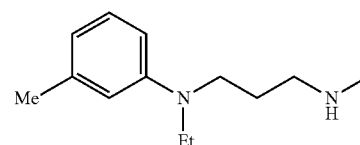
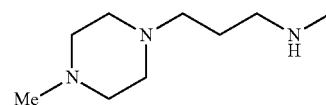
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442859-27-0

55

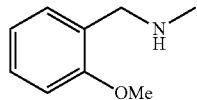
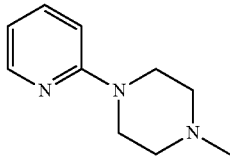
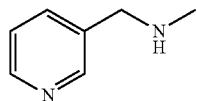
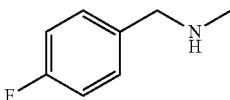
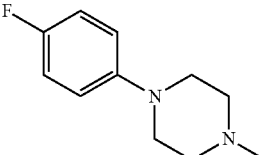
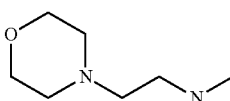
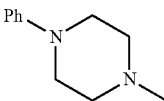
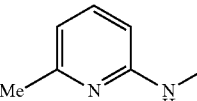
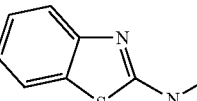
442859-26-9

65

R^aR^bN—

13

TABLE 9

442859-25-8	
442859-20-3	Et ₂ N—
442859-13-4	
442859-12-3	
442859-11-2	MeO—(CH ₂) ₃ —NH—
442859-09-8	nBuN(Et)—
442859-06-5	
442859-05-4	nBuNH—
442859-03-2	
442859-02-1	EtO ₂ C—CH ₂ —NH—
442859-01-0	MeO—(CH ₂) ₂ —NH—
442859-99-3	nBuN(Me)NH—
442858-98-2	
442858-93-7	Ph— 
442858-91-5	PhCH ₂ N(Me)—
442858-86-8	
442858-79-9	

14

TABLE 10

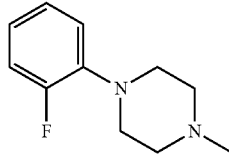
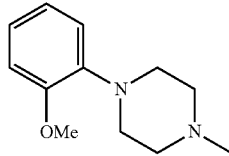
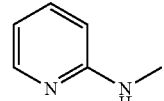
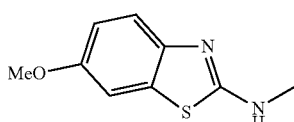
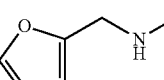
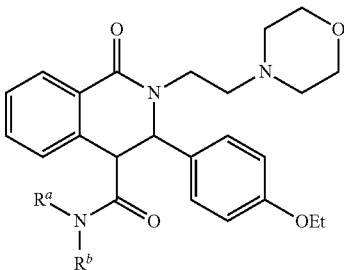
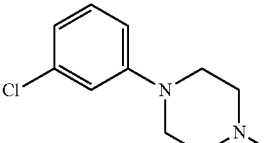
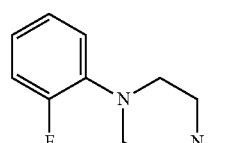
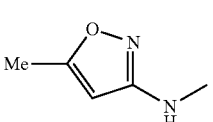
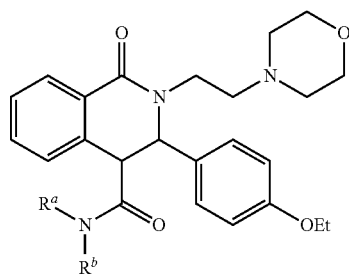
442858-77-7	
442858-76-6	
442858-72-2	
442858-67-5	
442858-56-2	iPrNH—
442858-55-1	

TABLE 11

	
CAS Registry No.	R ^a R ^b N—
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442888-70-2	
442888-60-0	

15

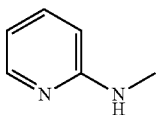
TABLE 11-continued



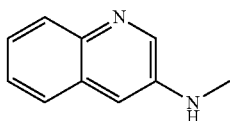
CAS Registry No.

R^aR^bN—

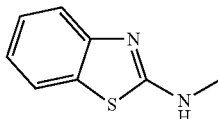
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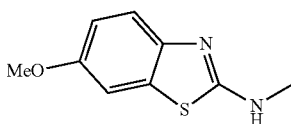
442888-41-7



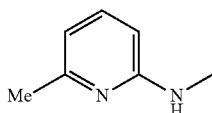
442888-39-3



442888-37-1



442888-35-9



Non-Patent Document 1: "American Journal of Gastroenterology", (USA), 2003, vol. 98, p. 750-758

Non-Patent Document 2: "Gut", (England), 1998, vol. 42, p. 845-849

Non-Patent Document 3: "The Journal of Neuroscience", (USA), 1998, vol. 18, p. 4758-4766

Non-Patent Document 4: "Life Sciences", (Holland), 2002, vol. 70, p. 2953-2966

Non-Patent Document 5: "Gastroenterology", (USA), 1991, vol. 100, p. 980-985

Non-Patent Document 6: "Neurogastroenterology and Motility", (England), 1997, vol. 9, p. 265-270

Non-Patent Document 7: "Annals of the New York Academy of Science", (USA), 2000, vol. 921, p. 420-424

Non-Patent Document 8: "Cancer", (USA), 1998, vol. 83, p. 1335-1343

Non-Patent Document 9: "British Journal of Cancer", 2000, vol. 83, p. 906-913,

Non-Patent Document 10: "Cancer", (USA), 2000, vol. 88, p. 1384-1392

Patent Document 1: Pamphlet of International Publication No. 2006/115135

Patent Document 2: Pamphlet of International Publication No. 2004/04727

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Patent Document 3: Pamphlet of International Publication No. 2006/97323

Patent Document 4: Pamphlet of International Publication No. 03/29221

DISCLOSURE OF THE INVENTION

Problem that the Invention is to Solve

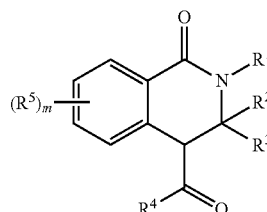
It is an object of the present invention to provide a novel pharmaceutical having a BB2 receptor antagonistic action, in particular, a novel compound which is useful as a therapeutic agent for IBS.

Means for Solving the Problems

The present inventors have conducted extensive studies on BB2 receptor antagonists, and as a result, we have found that a novel tetrahydroisoquinolin-1-one derivative having an amide group as a substituent at the 4-position has an excellent BB2 receptor antagonistic action, thus completing the present invention.

Namely the present invention relates to a tetrahydroisoquinolin-1-one derivative represented by the general formula (I) or a pharmaceutically acceptable salt thereof:

[Chem. 4]



(I)

[the symbols in the formula represent the following meanings:

R¹: lower alkylene-OH, lower alkylene-N(R⁰)(R⁶), lower alkylene-CO₂R⁰, cycloalkyl, cycloalkenyl, aryl, heterocyclic group, -(lower alkylene substituted with —OR⁰)-aryl or lower alkylene-heterocyclic group,

wherein the lower alkylene, cycloalkyl, cycloalkenyl, aryl and heterocyclic group in R¹ may each be substituted,

R⁰: the same as or different from each other, each representing —H or lower alkyl,

R⁶: R⁰, —C(O)—R⁰, —CO₂-lower alkyl or —S(O)₂-lower alkyl,

R²: lower alkyl, lower alkylene-OR⁰, lower alkylene-aryl, lower alkylene-heterocyclic group, lower alkylene-N(R⁰)CO-aryl, lower alkylene-O-lower alkylene-aryl, —CO₂R⁰, —C(O)N(R⁰)₂, —C(O)N(R⁰)-aryl, —C(O)N(R⁰)-lower alkylene-aryl, aryl or heterocyclic group,

wherein the aryl and heterocyclic group in R² may each be substituted,

R³: —H or lower alkyl,

or R² and R³ may be combined to form C₂₋₆ alkylene,

R⁴: —N(R⁷)(R⁸), —N(R⁰)—OH, —N(R¹⁰)—OR⁷, —N(R⁰)—N(R⁰)(R⁷), —N(R⁰)—S(O)₂-aryl, or —N(R⁰)—S(O)₂—R⁷,

wherein the aryl in R⁴ may be substituted,

R⁷: lower alkyl, halogeno-lower alkyl, lower alkylene-CN, lower alkylene-OR⁰, lower alkylene-CO₂R⁰, lower alkylene-C(O)N(R⁰)₂, lower alkylene-C(O)N(R⁰)N(R⁰)₂, lower alky-

lene-C(=NH)NH₂, lower alkylene-C(=NOH)NH₂, heteroaryl, lower alkylene-X-aryl, or lower alkylene-X-heterocyclic group,

wherein the lower alkylene, aryl, heteroaryl, and heterocyclic group in R⁷ may each be substituted,

X: single bond, —O—, —C(O)—, —N(R⁰)—, —S(O)_p—, or *—C(O)N(R⁰)—,

wherein * in X represents a bond to lower alkylene,

m: an integer of 0 to 3,

p: an integer of 0 to 2,

R⁸: —H or lower alkyl,

or R⁷ and R⁸ may be combined to form lower alkylene-N(R⁹)-lower alkylene, lower alkylene-CH(R⁹)-lower alkylene, lower alkylene-arylene-lower alkylene, or lower alkylene-arylene-C(O)—,

R⁹: aryl and heteroaryl which may each be substituted,

R¹⁰: —H, lower alkyl, or —C(O)R⁰,

R⁵: lower alkyl, halogeno-lower alkyl, halogen, nitro, —OR⁰, —O-halogeno-lower alkyl, —N(R⁰)₂, —O-lower alkylene-CO₂R⁰, or —O-lower alkylene-aryl,

wherein the aryl in R⁵ may be substituted,

provided that, when R⁴ is —N(R⁷)(R⁸),

(1) a compound wherein R¹ is unsubstituted cyclopentyl and R² is unsubstituted 2-thienyl;

(2) a compound wherein R¹ is unsubstituted cyclohexyl and R² is 4-methoxyphenyl;

(3) a compound wherein R¹ is 4-methoxyphenyl and R² is 4-methoxyphenyl; and

(4) a compound wherein R¹ is (morpholin-4-yl)ethyl and R² is 4-ethoxyphenyl are excluded,

furthermore, 2,3-bis(4-chlorophenyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-(4-chlorobenzyl)-2-(4-chlorophenyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-2-cyclopropyl-N-(2-furylmethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-2-cyclopropyl-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

ethyl 3-{3-[3,5-bis(trifluoromethyl)phenyl]-4-{[2-(4-methoxyphenyl)ethyl]carbamoyl}-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl}propanoate,

N-benzyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-oxo-2-(tetrahydrofuran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-N-(2-methoxyethyl)-2-(2-morpholin-4-ylethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-2-(2-furylmethyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-N-(2-furylmethyl)-2-(2-morpholin-4-ylethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide, and

(4-chlorophenyl)[3-(4-chlorophenyl)-4-[(2-methoxyethyl)carbamoyl]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]acetic acid are excluded.

The symbols hereinafter represent the same meanings].

Further, the present application relates to a pharmaceutical comprising a tetrahydroisoquinolin-1-one derivative represented by the general formula (I) or a salt thereof as an active ingredient, in particular a BB2 receptor antagonist, a therapeutic agent for irritable bowel syndrome or a therapeutic agent for cancers.

Furthermore, the present application relates to the use of the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a BB2 receptor antagonist, a therapeutic agent for irritable bowel syndrome, or a therapeutic agent for cancers, and to a method for treating irritable bowel syndrome or cancers, comprising administering to a patient an effective amount of the compound represented by the formula (I) or a pharmaceutically acceptable salt thereof.

Namely, the present application relates to: (1) a pharmaceutical composition comprising the compound described in the general formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier,

(2) the pharmaceutical composition as described in (1), which is a BB2 receptor antagonist,

(3) the pharmaceutical composition as described in (1), which is a therapeutic agent for irritable bowel syndrome,

(4) the pharmaceutical composition as described in (1), which is a therapeutic agent for cancers,

(5) use of the compound as described in the general formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a BB2 receptor antagonist, a therapeutic agent for irritable bowel syndrome, or a therapeutic agent for cancers, and

(6) a method for treating irritable bowel syndrome or cancers, comprising administering to a patient a therapeutically effective amount of the compound as described in the general formula (I) or a pharmaceutically acceptable salt thereof.

Effects of the Invention

The compound of the present invention is useful as a therapeutic agent for IBS since it has an excellent antagonistic action on a BB2 receptor.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention will be described in more detail as follows.

The “lower alkyl” is preferably a linear or branched alkyl having 1 to 6 carbon atoms (which is hereinafter simply referred to as C₁₋₆), and specifically, it includes methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, n-hexyl group, and the like. More preferably, it is C₁₋₄ alkyl, and more preferably, it includes methyl, ethyl, n-propyl, and isopropyl.

The “lower alkylene” is preferably a linear or branched C₁₋₆ alkylene, and specifically, it includes methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, propylene, methylenemethylene, ethylethylene, 1,2-dimethylethylene, 1,1,2,2-tetramethylethylene group, and the like. Preferably, it is C₁₋₄ alkylene, and more preferably, it includes methylene, ethylene, and trimethylene.

The “halogen” means F, Cl, Br, or I.

The “halogeno-lower alkyl” refers to C₁₋₆ alkyl substituted with one or more halogens. It is preferably lower alkyl substituted with 1 to 5 halogens, and more preferably trifluoromethyl.

The “halogen-lower alkylene” refers to C₁₋₆ alkylene substituted with one or more halogens. It is preferably lower alkylene substituted with 1 to 5 halogens, and more preferably, it includes difluoromethylene and difluoroethylene.

The “cycloalkyl” refers to a C₃₋₁₀ saturated hydrocarbon ring group, which may have a bridge. Specifically, it includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl group, and the like. It is preferably

C₃₋₈ cycloalkyl, and more preferably C₃₋₆ cycloalkyl, and even more preferably, it includes cyclopentyl and cyclohexyl.

The "cycloalkenyl" refers to C₃₋₁₅ cycloalkenyl, which may have a bridge, and it includes a ring group condensed with a benzene ring at a double bond site. Specifically, it includes cyclopentenyl, cyclopentadienyl, cyclohexenyl, cyclohexadienyl, 1-tetrahydronaphthyl, 1-indenyl, 9-fluorenyl group, and the like. Preferably, it is C₅₋₁₀ cycloalkenyl, and more preferably, it includes cyclopentenyl and cyclohexenyl.

The "aryl" refers to a C₆₋₁₄ monocyclic to tricyclic aromatic hydrocarbon ring group, and preferably, it includes phenyl and naphthyl, and more preferably phenyl.

The "arylene" refers to a divalent group formed by removing an arbitrary hydrogen atom from aryl, and it is preferably phenylene, and more preferably orthophenylene.

The "heteroaryl" means a ring group consisting of i) monocyclic 5- to 6-membered heteroaryl containing 1 to 4 hetero atoms selected from O, S, and N, and ii) bicyclic a 8- to 10-membered heterocycle and a tricyclic 11- to 14-membered heterocycle, each containing 1 to 5 hetero atoms selected from O, S, and N, which are formed by condensation of the monocyclic heteroaryl, and one or two rings selected from the group consisting of monocyclic heteroaryl and a benzene ring. The ring atom S or N may be oxidized to form an oxide or a dioxide.

The "heteroaryl" preferably includes pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, indolyl, indazolyl, benzoimidazolyl, imidazopyridyl, quinolyl, quinoxalyl, quinoxalyl, naphthylidyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, and carbazolyl, and more preferably pyrrolyl, pyridyl, furyl, thienyl, and thiazolyl.

The "heterocyclic group" means a ring group consisting of i) a monocyclic 3- to 8-membered (preferably 5- to 7-membered) heterocycle containing 1 to 4 hetero atoms selected from O, S, and N, and ii) a bicyclic 8- to 14-membered (preferably 9- to 11-membered) heterocycle and a tricyclic 11- to 20-membered (preferably 12- to 15-membered) heterocycle, each containing 1 to 5 hetero atoms selected from O, S, and N, which are formed by the condensation of the monocyclic heterocycle, and one or two rings selected from the group consisting of a monocyclic heterocycle, a benzene ring, C₅₋₈ cycloalkane, and C₅₋₈ cycloalkene. The ring atom S or N may be oxidized to form an oxide or a dioxide, or may have a bridge.

The "heterocyclic group" preferably includes aziridinyl, azetidyl, pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl, oxiranyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranal, morpholinyl, homomorpholinyl, tetrahydrothienyl, tetrahydrothiopyranal, thiomorpholinyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, pyridyl, pyrimidinyl, pyrazinyl, furyl, thienyl, oxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, indolyl, indazolyl, benzimidazolyl, imidazopyridyl, quinolyl, quinoxalyl, quinoxalyl, naphthylidyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, dihydroindolyl, dihydrobenzimidazolyl, dihydrobenzofuranyl, tetrahydroquinolyl, benzodioxolyl, dihydrobenzodioxynyl, dihydrobenzoxazinyl, tetrahydronaphthylidyl, carbazolyl, and quinuclidyl, and more preferably pyrrolidinyl, piperidinyl, tetrahydrofuryl, tetrahydropyranal, pyrrolyl, pyridyl, furyl, thienyl, and thiazolyl.

The expression "which may be substituted" means "which is not substituted" or "which is substituted with 1 to 5 substituents which may be the same as or different from each other". The expression "which is substituted" refers to

"which is substituted with 1 to 5 substituents which are the same as or different from each other". Further, if a plurality of substituents are contained, the substituents may be the same as or different from each other.

The substituent for the "lower alkylene" which may be substituted in R¹ is preferably a group selected from Group G¹, and more preferably —OH or phenyl.

Group G¹: halogen, —OR⁰, —N(R⁰)(R⁶), and aryl.

Provided that, the "aryl" in Group G¹ may be substituted with a group selected from the group consisting of halogen, lower alkyl, halogeno-lower alkyl, —OR⁰, and —O-halogeno-lower alkyl.

The substituent for the "cycloalkyl", "cycloalkenyl", and "heterocyclic group" which may be each substituted in R¹ is preferably a group selected from Group G², more preferably —OR⁰, —CO₂R⁰, —N(R⁰)₂, —N(R⁰)C(O)R⁰, —N(R⁰)C(O)-lower alkylene-OR⁰, or —N(R⁰)S(O)₂-lower alkyl, and even more preferably —OR⁰, —N(R⁰)C(O)R⁰, or —N(R⁰)S(O)₂-lower alkyl.

Group G²: halogen, lower alkyl, halogeno-lower alkyl, lower alkylene-OR⁰, —OR⁰, —O-halogeno-lower alkyl, —N(R⁰)₂, —N(R⁰)-lower alkylene-OR⁰, —N(R⁰)-lower alkylene-CO₂R⁰, —N(R⁰)C(O)R⁰, —N(R⁰)C(O)OR⁰, —N(R⁰)C(O)-aryl, —N(R⁰)C(O)-lower alkylene-OR⁰, —N(R⁰)C(O)-lower alkylene-N(R⁰)₂, —N(R⁰)C(O)N(R⁰)₂, —N(R⁰)C(=N(R⁰))-lower alkyl, —N(R⁰)S(O)₂-lower alkyl, —N(lower alkylene-OR⁰)-S(O)₂-lower alkyl, —N(lower alkylene-CO₂R⁰)-S(O)₂-lower alkyl, —N(R⁰)S(O)₂-lower alkylene-CO₂R⁰, —N(R⁰)S(O)₂-lower alkylene-S(O)₂-lower alkyl, —N(R⁰)S(O)₂-aryl, —N(R⁰)S(O)₂N(R⁰)₂, —S(O)₂-lower alkyl, —CO₂R⁰, —CO₂-lower alkylene-Si(lower alkyl)₃, —C(O)N(R⁰)₂, —C(O)N(R⁰)-lower alkylene-OR⁰, —C(O)N(R⁰)-lower alkylene-N(R⁰)₂, —C(O)N(R⁰)-lower alkylene-CO₂R⁰, —C(O)N(R⁰)-O-lower alkylene-heterocyclic group, heterocyclic group, —C(O)R⁰, —C(O)-lower alkylene-OR⁰, —C(O)-lower alkylene-N(R⁰)₂, —C(O)-heterocyclic group, and oxo.

Provided that the "aryl" and the "heterocyclic group" in Group G² may be each substituted with a group selected from the group consisting of halogen, lower alkyl, halogeno-lower alkyl, —OR⁰, —O-halogeno-lower alkyl, and oxo.

The substituent for the "aryl" which may be substituted in R¹ is preferably a group selected from Group G³, and more preferably —OR⁰ or lower alkylene-OR⁰.

Group G³: halogen, lower alkyl, halogeno-lower alkyl, —OR⁰, —O-halogeno-lower alkyl, lower alkylene-OR⁰, and —CO₂R⁰.

The substituent for the "aryl" and the "heterocyclic group" which may be substituted in R² is preferably a group selected from Group G⁴, more preferably halogen, lower alkyl, or —OR⁰, and even more preferably halogen.

Group G⁴: halogen, —CN, nitro, lower alkyl, halogeno-lower alkyl, —OR⁰, —N(R⁰)₂, —CO₂R⁰, —C(O)N(R⁰)₂, —OS(O)₂-lower alkyl, and oxo.

The substituent for the "lower alkylene" which may be substituted in R⁷ is preferably a group selected from Group G⁵, more preferably halogen.

Group G⁵: halogen, —OR⁰, —N(R⁰)₂, and aryl.

Provided that the "aryl" in Group G⁵ may be substituted with a group selected from the group consisting of halogen, lower alkyl, halogeno-lower alkyl, —OR⁰, and —O-halogeno-lower alkyl.

The substituent for the "aryl" and the "heterocyclic group" which may be each substituted in R⁷ is preferably a group selected from Group G⁶, and more preferably halogen, —OR⁰, lower alkylene-OR⁰, —CO₂R⁰, lower alkylene-CO₂R⁰, —O-lower alkylene-CO₂R⁰, or oxo.

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Group G^6 : halogen, lower alkyl which may be substituted with $-\text{OR}^0$, halogeno-lower alkyl which may be substituted with $-\text{OR}^0$, $-\text{OR}^0$, $-\text{CN}$, $-\text{N}(\text{R}^0)_2$, $-\text{CO}_2\text{R}^0$, $-\text{CO}_2$ -lower alkylene-aryl, $-\text{C}(\text{O})\text{N}(\text{R}^0)_2$, lower alkylene- $\text{OC}(\text{O})\text{R}^0$, lower alkylene- $\text{OC}(\text{O})\text{aryl}$, lower alkylene- CO_2R^0 , halogeno-lower alkylene- CO_2R^0 , lower alkylene- CO_2 -lower alkylene-aryl, lower alkylene- $\text{C}(\text{O})\text{N}(\text{R}^0)_2$, halogeno-lower alkylene- $\text{C}(\text{O})\text{N}(\text{R}^0)_2$, $-\text{O}$ -lower alkylene- CO_2R^0 , $-\text{O}$ -lower alkylene- CO_2 -lower alkylene-aryl, $-\text{O}$ -lower alkylene- $\text{C}(\text{O})\text{N}(\text{R}^0)_2$, $-\text{O}$ -halogeno-lower alkylene- CO_2R^0 , $-\text{O}$ -halogeno-lower alkylene- $\text{C}(\text{O})\text{N}(\text{R}^0)_2$, $-\text{C}(\text{O})\text{N}(\text{R}^0)\text{S}(\text{O})_2$ -lower alkyl, lower alkylene- $\text{C}(\text{O})\text{N}(\text{R}^0)\text{S}(\text{O})_2$ -lower alkyl, $-\text{S}(\text{O})_2$ -lower alkyl, $-\text{S}(\text{O})_2\text{N}(\text{R}^0)_2$, heterocyclic group, $-\text{C}(=\text{NH})\text{NH}_2$, $-\text{C}(=\text{NH})=\text{NO}-\text{C}(\text{O})\text{O}-\text{C}_{1-10}$ alkyl, $-\text{C}(=\text{NOH})\text{NH}_2$, $-\text{C}(\text{O})\text{N}=\text{C}(\text{N}(\text{R}^0)_2)_2$, $-\text{N}(\text{R}^0)\text{C}(\text{O})\text{R}^0$, $-\text{N}(\text{R}^0)\text{C}(\text{O})$ -lower alkylene- OR^0 , $-\text{N}(\text{R}^0)\text{C}(\text{O})\text{OR}^0$, $-\text{N}(\text{R}^0)\text{S}(\text{O})_2$ -lower alkyl, $-\text{C}(\text{aryl})_3$, and oxo.

Provided that the "aryl" and the "heterocyclic group" in Group G^6 may each be substituted with a group selected from the group consisting of halogen, lower alkyl, halogeno-lower alkyl, $-\text{OR}^0$, $-\text{O}$ -halogeno-lower alkyl, oxo, and thioxo ($=\text{S}$).

The substituent for the "aryl" which may be substituted in R^4 ; and the substituent for the "heteroaryl" which may be substituted in R^7 are preferably a group selected from the group consisting of halogen, lower alkyl, halogeno-lower alkyl, $-\text{OR}^0$, and $-\text{O}$ -halogeno-lower alkyl.

The substituent for the "aryl" and "heteroaryl" which may be each substituted in R^9 is preferably a group selected from the group consisting of halogen, lower alkyl, halogeno-lower alkyl, $-\text{OR}^0$, and $-\text{O}$ -halogeno-lower alkyl.

The substituent for the "aryl" which may each be substituted in R^5 is preferably a group selected from the group consisting of halogen, lower alkyl, halogeno-lower alkyl, $-\text{OR}^0$, and $-\text{O}$ -halogeno-lower alkyl.

Preferred embodiments of the present invention will be described below.

(a) R^1 is preferably (lower alkylene which may be substituted)-OH, or cycloalkyl, aryl, or a heterocyclic group, which may each be substituted. More preferably, it is (lower alkylene which may be substituted)-OH, or cyclopentyl, cyclohexyl, phenyl, tetrahydrofuryl, tetrahydropyranyl, pyrrolidyl, or piperidyl, which may be each substituted. More preferably, it is (lower alkylene which may be substituted with a group selected from the group consisting of phenyl which may be substituted with halogen, lower alkyl, or $-\text{OR}^0$, and $-\text{OH}$)-OH, or cycloalkyl substituted with a group selected from the group consisting of $-\text{OR}^0$, $-\text{N}(\text{R}^0)_2$, $-\text{N}(\text{R}^0)\text{C}(\text{O})\text{R}^0$, $-\text{N}(\text{R}^0)\text{C}(\text{O})$ -lower alkylene- OR^0 , $-\text{N}(\text{R}^0)\text{S}(\text{O})_2$ -lower alkyl, and a heterocyclic group. Even more preferably, it is (lower alkylene which may be substituted with a group selected from the group consisting of phenyl which may be substituted with halogen, lower alkyl or $-\text{OR}^0$, and $-\text{OH}$)-OH, or cyclopentyl or cyclohexyl, which is each substituted with a group selected from the group consisting of $-\text{OR}^0$, $-\text{N}(\text{R}^0)_2$, $-\text{N}(\text{R}^0)\text{C}(\text{O})\text{R}^0$, $-\text{N}(\text{R}^0)\text{C}(\text{O})$ -lower alkylene- OR^0 , $-\text{N}(\text{R}^0)\text{S}(\text{O})_2$ -lower alkyl and a heterocyclic group.

Particularly preferably, it is cyclohexyl substituted with a group selected from the group consisting of $-\text{OR}^0$, $-\text{N}(\text{R}^0)\text{C}(\text{O})\text{R}^0$, and $-\text{N}(\text{R}^0)\text{S}(\text{O})_2$ -lower alkyl.

(b) R^2 is preferably aryl which may be substituted, and more preferably phenyl which may be substituted with halogen, lower alkyl, or $-\text{OR}^0$, and even more preferably phenyl substituted with halogen.

(c) R^3 is preferably $-\text{H}$.

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(d) R^4 is preferably $-\text{N}(\text{R}^0)$ -lower alkylene-(aryl or heteroaryl, which may be each substituted) or $-\text{N}(\text{R}^0)-\text{O}$ -lower alkylene-(aryl or heteroaryl, which may be each substituted). More preferably, it is $-\text{NH}$ -lower alkylene-(phenyl, pyridyl, N-oxidopyridyl, thienyl, or thiazolyl, which may each be substituted) or $-\text{NH}-\text{O}$ -lower alkylene-(phenyl, pyridyl, N-oxidopyridyl, thienyl, or thiazolyl, which may be each substituted). More preferably, it is $-\text{NH}$ -lower alkylene-(phenyl, pyridyl, N-oxidopyridyl, thienyl, or thiazolyl, which may each be substituted with a group selected from the group consisting of halogen, $-\text{OR}^0$, lower alkylene- OR^0 , $-\text{CO}_2\text{R}^0$, lower alkylene- CO_2R^0 , and $-\text{O}$ -lower alkylene- CO_2R^0) or $-\text{NH}-\text{O}$ -lower alkylene-(phenyl, pyridyl, N-oxidopyridyl, thienyl, or thiazolyl, which may each be substituted with a group selected from the group consisting of halogen, $-\text{OR}^0$, lower alkylene- OR^0 , $-\text{CO}_2\text{R}^0$, lower alkylene- CO_2R^0 , and $-\text{O}$ -lower alkylene- CO_2R^0). Even more preferably, it is $-\text{NH}$ -lower alkylene-(phenyl which may be substituted with a group selected from the group consisting of halogen, $-\text{OR}^0$, lower alkylene- OR^0 , $-\text{CO}_2\text{R}^0$, lower alkylene- CO_2R^0 , and $-\text{O}$ -lower alkylene- CO_2R^0) or $-\text{NH}-\text{O}$ -lower alkylene-(phenyl which may be substituted with a group selected from the group consisting of halogen, $-\text{OR}^0$, lower alkylene- OR^0 , $-\text{CO}_2\text{R}^0$, lower alkylene- CO_2R^0 , and $-\text{O}$ -lower alkylene- CO_2R^0).

(e) R^5 is preferably halogen or $-\text{OR}^0$.

(f) m is preferably 0 or 1, and more preferably 0.

In further preferred embodiments, the compounds having any combination of each of the preferable groups as described in (a) to (f) above are preferred.

Furthermore, other preferred embodiments for the compound of the present invention represented by the general formula (I) are shown below.

(1) A compound represented by the general formula (I), wherein R^3 is $-\text{H}$.

(2) The compound as described in (1), wherein R^2 is phenyl which may be substituted with halogen, lower alkyl, or $-\text{OR}^0$.

(3) The compound as described in (2), wherein R^4 is $-\text{N}(\text{R}^0)$ -lower alkylene-(aryl or heteroaryl, which may each be substituted), or $-\text{N}(\text{R}^0)-\text{O}$ -lower alkylene-(aryl or heteroaryl, which may each be substituted).

(4) The compound as described in (3), wherein R^1 is (lower alkylene which may be substituted with a group selected from the group consisting of phenyl which may be substituted with halogen, lower alkyl or $-\text{OR}^0$, and $-\text{OH}$)-OH; or cycloalkyl substituted with a group selected from the group consisting of $-\text{OR}^0$, $-\text{N}(\text{R}^0)_2$, $-\text{N}(\text{R}^0)\text{C}(\text{O})\text{R}^0$, $-\text{N}(\text{R}^0)$ -lower alkylene- OR^0 , $-\text{N}(\text{R}^0)\text{S}(\text{O})_2$ -lower alkyl, and a heterocyclic group.

(5) A compound represented by the general formula (I) selected from the group consisting of:

(3R,4R)-3-(2,4-dichlorophenyl)-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide, (3R,4R)-3-(2,4-dichlorophenyl)-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-N-[(1-oxido-1,2,3,4-tetrahydroisoquinoline-4-carboxamide)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide], 3-[[{[(3R,4R)-3-(2,4-dichlorophenyl)-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino}oxy]methyl]benzoic acid, (4-[[{[(3R,4R)-3-(2,4-dichlorophenyl)-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino}oxy]methyl]phenyl)acetic acid,

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(3-[[[(3R,4R)-3-(2,4-dichlorophenyl)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino)oxy]methyl]phenoxy)acetic acid,
 {3-[2-[[[(3R,4R)-3-(2,4-dichlorophenyl)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]ethyl]phenyl}(difluoro)acetic acid,
 (3R,4R)-3-(2,4-dichlorophenyl)-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-N-(2-{3-[(methylsulfonyl)carbamoyl]phenyl}ethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 {4-[2-[[[(3R,4R)-3-(2,4-dichlorophenyl)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]ethyl]phenyl}acetic acid, and
 4-(3-[[[(3R,4R)-3-(2,4-dichlorophenyl)-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]oxy]methyl]phenoxy)butanoic acid;
 or a pharmaceutically acceptable salt thereof.

Furthermore, in the present specification, the “irritable bowel syndrome” (which is hereinafter referred to as IBS) includes diarrhea type IBS, constipation type IBS, and alternating type IBS. The disease to which the therapeutic agent of the present invention is applied is preferably diarrhea type IBS or alternating type IBS, and particularly preferably diarrhea type IBS.

The compounds of the present invention may exist in the form of other tautomers or geometrical isomers depending on the kind of the substituents. In the present specification, the compound may be described in only one form of an isomer, but the present invention includes the isomers, an isolated form or a mixture of the isomers.

Furthermore, the compound (1) may have asymmetric carbons or axial asymmetries, and correspondingly, it may exist in the form of optical isomers such as an (R)-form, an (S)-form, and the like. The compound of the present invention includes both a mixture and an isolated form of these optical isomers.

In addition, a pharmaceutically acceptable prodrug of the compound (1) is also included in the present invention. The pharmaceutically acceptable prodrug refers to a compound, having a group which can be converted into an amino group, OH, CO₂H, and the like of the present invention, by solvolysis or under a physiological condition. Examples of the group which forms the prodrug include those as described in Prog. Med., 5, 2157-2161 (1985), or “Pharmaceutical Research and Development” (Hirokawa Publishing Company, 1990), vol. 7, Drug Design, 163-198.

Furthermore, the compound of the present invention may form an acid-addition salt or a salt with a base, depending on the kind of the substituents, and these salts are included in the present invention as long as they are pharmaceutically acceptable salts. Specifically, examples thereof include acid addition salts with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, phosphoric acid, and the like, and with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid, tartaric acid, citric acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, aspartic acid, glutamic acid, or the like, and salts with inorganic bases such as sodium, potassium, magnesium, calcium, aluminum, and the like, and with organic bases such as methylamine, ethylamine, ethanolamine, lysine, ornithine, and the like, ammonium salts.

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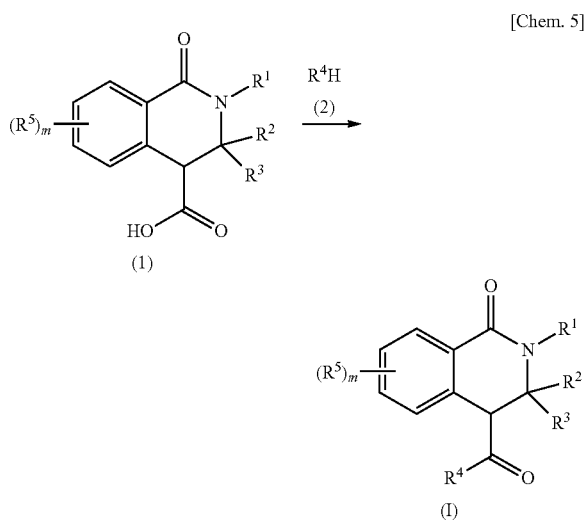
In addition, the present invention also includes various hydrates and solvates, and polymorphism of the compound of the present invention and a pharmaceutically acceptable salt thereof. Furthermore, the present invention also includes the compounds that are labeled with various radioactive or non-radioactive isotopes.

(Production Process)

The compound of the present invention and a pharmaceutically acceptable salt thereof may be prepared by applying various known synthetic methods, by the use of the characteristics based on their basic backbones or the kind of the substituents. Here, depending on the kind of the functional groups, it is in some cases effective from the viewpoint of the preparation techniques to substitute the functional group with an appropriate protecting group (a group which may be easily converted into the functional group), during the steps from starting materials to intermediates. Examples of such functional groups include an amino group, a hydroxyl group, a carboxyl group, and the like, and examples of a protecting group thereof include those as described in “Protective Groups in Organic Synthesis” (3rd edition, 1999), edited by Greene and Wuts, which may be optionally selected and used in response to the reaction conditions. By such a method, a desired compound can be obtained by introducing the protecting group and carrying out the reaction, and then, if desired, removing the protecting group.

In addition, a prodrug of the compound (1) can be prepared by introducing a specific group during the steps from starting materials to intermediates, in the same manner as for the aforementioned protecting groups, or by carrying out the reaction using the obtained compound (1). The reaction may be carried out by employing a method known to a person skilled in the art, such as general esterification, amidation, and dehydration.

Hereinbelow, the representative production processes of the compounds of the present invention will be described. Each of the production processes can also be carried out with reference to the reference documents attached to the present description. Further, the production processes of the present invention are not limited to the examples as shown below. (Production Process 1)



This production process is a process for obtaining the compound (1) of the present invention by subjecting a carboxylic acid compound (1) and an amine compound (2) to amidation.

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The reaction can be carried out using equivalent amounts of the carboxylic acid compound (1) and the amine compound (2), or an excess amount of either, and stirring them from under cooling to under heating, preferably at $-20^{\circ}\text{C}.$ to $60^{\circ}\text{C}.$, usually for 0.1 hour to 5 days, in a solvent which is inert to the reaction, in the presence of a condensing agent. The solvent as used herein is not particularly limited, but examples thereof include aromatic hydrocarbons such as benzene, toluene, xylene, and the like, halogenated hydrocarbons, such as dichloromethane, 1,2-dichloroethane, chloroform, and the like, ethers such as diethyl ether, tetrahydrofuran (THF), dioxane, dimethoxyethane, and the like, N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N-methylpyrrolidin-2-one (NMP), dimethyl sulfoxide (DMSO), ethyl acetate, acetonitrile, water, and the like, or mixture thereof. Examples of the condensing agent include 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC), dicyclohexylcarbodiimide, 1,1'-carbonyldiimidazole (CDI), diphenyl phosphoryl azide, phosphorous oxychloride, and the like, but are not limited to these. An additive (for example, 1-hydroxybenzotriazole (HOBt), and the like) may be preferable for the reaction in some cases. It may be advantageous for the smooth progress of the reaction to carry out the reaction in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, pyridine, N,N-dimethyl-4-aminopyridine (DMAP), and the like, or an inorganic base such as potassium carbonate, sodium carbonate, potassium hydroxide, and the like in some cases.

In addition, a process in which the carboxylic acid compound (1) is derived into a reactive derivative, and then reacted with the amine compound (2) can also be used. Examples of the reactive derivative of the carboxylic acid as used herein include an acid halide obtained by the reaction with a halogenating agent such as phosphorous oxychloride, thionyl chloride, and the like, a mixed acid anhydride obtained by the reaction with isobutyl chloroformate, or the like, an active ester obtained by the condensation with 1-hydroxybenzotriazole or the like, and others. The reaction of the reactive derivative and the amine compound (2) can be carried out from under cooling to under heating, preferably at $-20^{\circ}\text{C}.$ to $60^{\circ}\text{C}.$, in a solvent which is inert to the reaction, such as halogenated hydrocarbons, aromatic hydrocarbons, ethers, and the like.

Production Process 2: Other Production Processes

Furthermore, some compounds represented by the formula (I) can also be prepared by subjecting the compound of the present invention obtained as above to any combination of the processes that are usually employed by a skilled person in the art, such as conventional amidation, hydrolysis, N-oxidation, reductive amination, sulfonylation, oxidation, reduction, N-alkylation, O-alkylation, and the like. For example, they can be prepared by the reactions as below, the methods described in Examples to be described later, a method apparent to a skilled person in the art, or a modified method thereof.

2-1: Amidation

An amide compound can be obtained by subjecting a carboxylic acid compound and an amine compound to amidation.

The amidation can be carried out in the same manner as in Production Process 1.

2-2: Hydrolysis

A compound having a carboxyl group can be prepared by hydrolyzing a compound having an ester group.

The reaction can be carried out from under cooling to under heating in a solvent such as aromatic hydrocarbons, ethers, halogenated hydrocarbons, alcohols, DMF, DMA, NMP, DMSO, pyridine, water, and the like in the presence of an acid

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including mineral acids such as sulfuric acid, hydrochloric acid, hydrobromic acid, and the like, and organic acids such as formic acid, acetic acid, and the like; or in the presence of a base such as lithium hydroxide, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, cesium carbonate, ammonia, and the like.

2-3: N-oxidation

An N-oxide compound can be prepared by oxidating the nitrogen atom of a heterocycle having a nitrogen atom, such as pyridine and the like, with various oxidants.

The reaction can be carried out from under cooling, at room temperature to under heating, using an equivalent amount or excess amount of m-chloroperbenzoic acid, peracetic acid, aqueous hydrogen peroxide, and the like as an oxidant, in a solvent such as halogenated hydrocarbons, acetic acid, water, and the like.

2-4: Reductive Amination

An amine compound can be alkylated by reducing an imine compound which is prepared from a primary or secondary amine compound and a carbonyl compound.

The reaction can be carried out using equivalent amounts of an amine compound and a carbonyl compound, or an excessive amount of either thereof, in the presence of a reducing agent, in a solvent such as halogenated hydrocarbons, alcohols, ethers, and the like. As the reducing agent, sodium cyanoborohydride, sodium triacetoxymethylborohydride, sodium borohydride, and the like can be used. The reaction may be preferably carried out in the presence of an acid such as acetic acid, hydrochloric acid, titanium (IV) isopropoxide complexes, and the like in some cases.

2-5: Sulfonylation

A sulfonamide compound can be obtained by the sulfonylation of an amine compound.

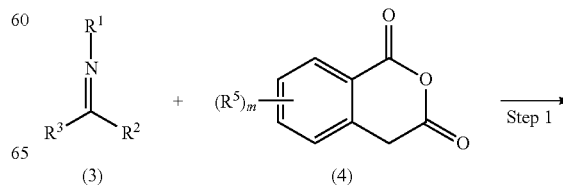
The reaction can be carried out, for example, from under cooling, at room temperature to under heating, by using equivalent amounts of an amine compound and a sulfonyl halide, or an excessive amount of either thereof, in a solvent such as aromatic hydrocarbons, ethers, halogenated hydrocarbons, pyridine, and the like. It may be advantageous for the smooth progress of the reaction to carry out the reaction in the presence of an organic base such as triethylamine, N,N-diisopropylethylamine, pyridine, and the like, or an inorganic base such as potassium carbonate, sodium carbonate, potassium hydroxide, and the like in some cases.

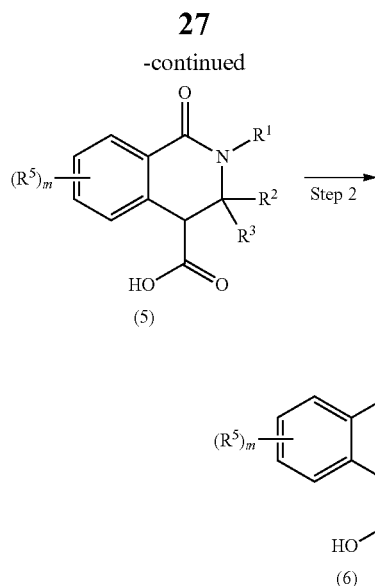
(Production Processes for Starting Compounds)

The starting material used for the preparation of the compound of the present invention can be prepared, for example, by applying the methods described below, the methods described in Production Examples to be described later, a known method, a method apparent to a skilled person in the art, or a modified method thereof.

(Starting Material Synthesis 1)

[Chem. 6]



**Step 1:**

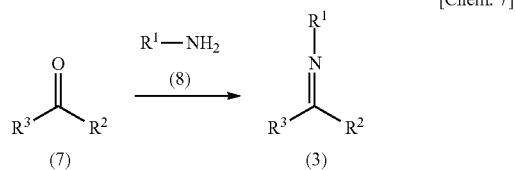
A compound (5) can be obtained by reacting a compound (3) with a compound (4).

The reaction can be carried out from at room temperature to under heating, using equivalent amounts of the compound (3) and the compound (4) or an excessive amount of either thereof, in a solvent such as ethers, halogenated hydrocarbons, aromatic hydrocarbons, and the like.

Step 2:

When R^3 is —H , a compound (6) in which the substituents at the 3- and 4-positions are trans can be obtained by isomerizing the compound (5).

The reaction can be carried out by treating the compound (5) with a base such as sodium hydroxide, potassium hydroxide, and the like, from at room temperature to under heating, in a solvent such as halogenated hydrocarbons, alcohols, water, and the like.

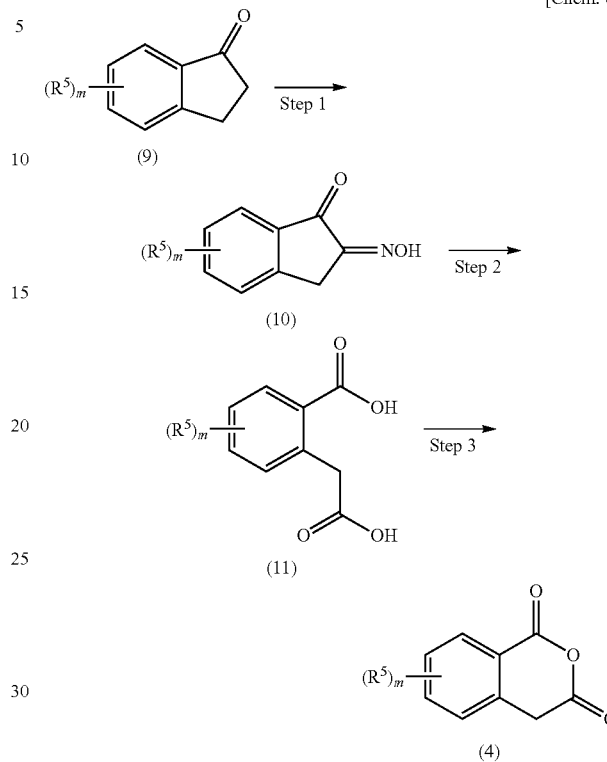
(Starting Material Synthesis 2)

The compound (3) can be obtained by carrying out dehydration-condensation of a compound (7) with a compound (8).

The reaction can be carried out from at room temperature to under heating, using equivalent amounts of the compound (7) and the compound (8) or an excessive amount of either thereof, in a solvent such as halogenated hydrocarbons, aromatic hydrocarbons, and the like. It may be advantageous for the smooth progress of the reaction to use a dehydrating agent such as anhydrous sodium sulfate, anhydrous magnesium sulfate, Molecular Sieves, and the like in some cases.

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(Starting Material Synthesis 3)

[Chem. 8]

**Step 1:**

A compound (10) can be obtained by reacting a compound (9) with a nitrite.

The reaction can be carried out from under cooling, at room temperature to under heating in a solvent such as ethers, halogenated hydrocarbons, alcohols, and the like in the presence of a nitrite such as ethyl nitrite, butyl nitrite, isoamyl nitrite, and the like. According to the compounds, it is advantageous for the progress of the reaction to carry out the reaction in the presence of an acid such as acetic acid, hydrochloric acid, and the like, or a base such as sodium methoxide, sodium ethoxide, potassium tert-butoxide, and the like in some cases.

Step 2

A compound (11) can be prepared by subjecting the compound (10) to rearrangement and then to hydrolysis.

The rearrangement reaction can be carried out by treating the compound (10) with thionyl chloride, or the like under cooling.

The hydrolysis reaction can be carried out from at room temperature to under heating, in a solvent such as alcohols, water, and the like, using a base such as sodium hydroxide, potassium hydroxide, and the like.

Step 3

The compound (4) can be obtained by the dehydration of the compound (11).

The dehydration reaction can be carried out from at room temperature to under heating, using acetyl chloride or the like as a dehydrating agent.

The compound of the present invention is isolated and purified as a free compound, a pharmaceutically acceptable salt, hydrate, solvate, or polymorphism thereof. The pharmaceutically acceptable salt of the compound (1) of the present invention can be prepared by a salt formation reaction within a conventional technology.

The isolation and purification can be carried out by employing general chemical operations such as extraction, fractional crystallization, various types of fractional chromatography, and the like.

Various isomers can be separated by selecting an appropriate starting compound, or by making use of the difference in the physicochemical properties between isomers. For example, the optical isomer can be derived into a stereochemically pure isomer by means of general optical resolution methods (for example, fractional crystallization for inducing to diastereomeric salts with optically active bases or acids, chromatography using a chiral column, etc., and the like). In addition, the isomers can also be prepared from an appropriate optically active starting compound.

The pharmacological activity of the compound of the present invention was confirmed by the following test.

Test Example 1

BB2 Receptor Antagonistic Activity

A BB2 receptor binding test was carried out using a membrane sample prepared from a human prostate cancer-derived PC-3 cell. The PC-3 cell was cultured using an RPMI-1640 medium containing 5% fetal bovine serum, and then a membrane sample was prepared by the following methods. The cells detached by a trypsin treatment were added with a 50 mM Tris-HCl buffer (pH 7.4, containing 0.2 mg/ml trypsin inhibitor and 0.2 mg/ml benzamidine), and homogenized by Polytron. The cell suspension was centrifuged at 1,500 rpm for 10 minutes, and the supernatant thus obtained was subjected to 1 hour of ultracentrifugation at 37,000×g. The precipitate was suspended in the aforementioned buffer to a concentration of 0.4 mg protein/ml, and stored at -80° C.

The BB2 receptor binding test was carried out by the following method, and the receptor antagonistic activity of a compound to be tested was calculated. A 50 µl of the membrane sample, 50 µl of an assay buffer (20 mM HEPES-HBSS containing 0.1% bovine serum albumin and 0.1 mg/ml bacitracin, pH 7.4), ¹²⁵I [Tyr⁴] bombesin (0.075 nM) and 2 µl of the compound to be tested dissolved in dimethyl sulfoxide were added to a 96 well assay plate, and incubated at room temperature for 2 hours. Non-specific binding was measured using 1 µM of bombesin. After completion of the incubation, the reaction solution was filtered through a Whatman GF/B filter which had been soaked in 0.5% polyethyleneimine. The radioactivity on the filter was measured using a microplate scintillation counter (Top Count, Perkin-Elmer Co., Ltd.). The 50% binding inhibition concentrations of the representative Example Compounds are shown in Table 12. Further, Ex represents the number of the Example compound.

TABLE 12

Ex	IC ₅₀ (nM)
61	12.8
62	18.3
236	3.0
542	4.7
560	4.8
589	5.7
631	4.5
700	6.7
701	7.4
709	8.9
712	6.7
856	6.8

Test Example 2

Restraint Stress-Induced Defecation Model

The compound to be tested of the present test was used by dissolving in water for injection containing 20% propylene glycol+20% Tween 80 or a 0.5% MC (methyl cellulose) solution.

Fifteen minutes after oral administration of the compound to be tested to a fed male Wistar rat, the animal was put into a restraint stress cage (KN-468, Natsume Seisakusho Co Ltd.). The number of feces excreted during a period from the restriction commencement to 1 hour thereafter was measured. Normal group was put into a separate cage, and number of feces excreted during 1 hour was measured in the same manner.

The inhibitory rates (%) of the representative Example Compounds when they were orally administered at a dose of 1 mg/kg are shown in Table 13. As a result, it was confirmed that the compound of the present invention exhibited an excellent action to improve the bowel movement symptom.

TABLE 13

Ex	Inhibitory Rate (%)
542	40.0
560	62.1
589	73.9
631	53.8
700	69.8
701	41.3
709	41.5
712	55.0
856	61.4

As a result of the test as described above, it was confirmed that the compound of the present invention has a BB2 receptor inhibitory action. From this point, it is obvious that the compound is useful as a therapeutic agent for the diseases associated with the BB2 receptors, in particular, IBS, cancers, functional dyspepsia, diabetic gastroparesis, reflux esophagitis, peptic ulcer, and the like.

The preparation containing one or two or more of the compound (1) of the present invention or a salt thereof as an active ingredient can be prepared in accordance with a generally used method, using a pharmaceutical carrier, an excipient, and the like, which are generally employed in the art.

The administration can be accompanied by any mode of oral administration via tablets, pills, capsules, granules, powders, liquid preparations, or the like; or parenteral administration via injections such as intraarticular, intravenous, or intramuscular injections, suppositories, eye drops, eye ointments, transdermal liquid preparations, ointments, transdermal patches, transmucosal liquid preparations, transmucosal patches, inhalations, and the like.

Regarding the solid composition for oral administration according to the present invention, tablets, powders, granules, or the like are used. In such a solid composition, one or two or more of active ingredients are mixed with at least one inactive excipient such as lactose, mannitol, glucose, hydroxypropylcellulose, microcrystalline cellulose, starch, polyvinyl pyrrolidone, and/or magnesium aluminometasilicate, and the like. According to a conventional method, the composition may contain inert additives such as a lubricant such as magnesium stearate, a disintegrator such as carboxymethyl starch sodium, a stabilizing agent, and a solubilizing agent. As necessary, tablets or pills may be coated with a sugar coating, or a film of a gastric or enteric material.

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The liquid composition for oral administration includes pharmaceutically acceptable emulsions, solutions, suspensions, syrups, elixirs, or the like, and contains a generally used inert diluent such as purified water and ethanol. In addition to the inert solvent, this liquid composition may contain an auxiliary agent such as a solubilizing agent, a moistening agent, and a suspending agent, a sweetener, a flavor, an aroma, and an antiseptic.

The injections for parenteral administration include sterile aqueous or non-aqueous liquid preparations, suspensions, and emulsions. As the aqueous solvent, for example, distilled water for injection and physiological saline are included. Examples of the non-aqueous solvent include propylene glycol, polyethylene glycol, plant oils such as olive oil, alcohols such as ethanol, and Polysorbate 80 (Japanese Pharmacopeia), and the like. Such a composition may further contain a tonicity agent, an antiseptic, a moistening agent, an emulsions, a dispersant, a stabilizer, or a solubilizing agent. These are sterilized, for example, by filtration through a bacteria retaining filter, blending of a bactericide, or irradiation. In addition, these can also be used by preparing a sterile solid composition, and dissolving or suspending in sterile water or a sterile solvent for injection prior to its use.

The drug for external use includes ointments, plasters, creams, jellies, cataplasms, sprays, lotions, eye drops, eye ointments, and the like. The drug contains generally used ointment bases, lotion bases, aqueous or non-aqueous solutions, suspensions, emulsions, and the like. Examples of the ointment or lotion bases include polyethylene glycol, propylene glycol, white vaseline, bleached beeswax, polyoxyethylene hydrogenated castor oil, glyceryl monostearate, stearyl alcohol, cetyl alcohol, laurmacrogol, sorbitan sesquioleate, and the like.

Regarding a transmucosal agent such as an inhalation, a transnasal agent, and the like, those in a solid, liquid, or semi-solid state are used, and may be produced in accordance with a conventionally known method. For example, a known excipient, and in addition, a pH adjusting agent, an antiseptic, a surfactant, a lubricant, a stabilizing agent, a thickening agent, and the like may be added thereto, if desired. For their administration, an appropriate device for inhalation or blowing may be used. For example, a compound may be administered alone or as a powder of formulated mixture, or as a solution or suspension in combination with a pharmaceutically acceptable carrier, using a conventionally known device or sprayer, such as a measured administration inhalation device and the like. The dry powder inhaler or the like may be for single or multiple administration use, and a dry powder or a powder-containing capsule may be used. Alternatively, this may be in a form such as a high pressurized aerosol spray which uses an appropriate propellant, for example, a suitable gas such as chlorofluoroalkane, hydrofluoroalkane, carbon dioxide, and the like.

In the case of conventional oral administration, the daily dose may be generally from about 0.001 to 100 mg/kg, preferably from 0.1 to 30 mg/kg, and even more preferably 0.1 to 10 mg/kg, per body weight, and this is administered in one portion or in 2 to 4 divided portions. Also, in the case of intravenous administration, the daily dose is from about 0.0001 to 10 mg/kg per body weight, once a day or twice or more times a day. In addition, a transmucosal agent is administered at a dose from about 0.001 to 100 mg/kg per body weight, once a day or twice or more times a day. The dose is appropriately decided in response to an individual case by taking symptoms, age, gender, or the like into consideration.

The compound of the present invention can be used in combination with various therapeutic or prophylactic agents

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for the diseases, for which the compound of the present invention is considered effective. The combined preparation may be administered simultaneously, or separately and continuously or at a desired time interval. The preparations to be co-administered may be a blend, or prepared individually.

EXAMPLES

Hereinbelow, the production processes for the compound (1) of the present invention will be described in more detail with reference to Examples. The compound of the present invention is not limited to the compounds described in Examples below. Further, the production processes for the starting compounds will be described in Production Examples.

In addition, the following abbreviations are used in Examples, Production Examples, and Tables to be described later.

PEX: Production Example, Ex: Example, No: Compound No., Data: Physicochemical Data (EI+: m/z value in EI-MS (cation) (unless otherwise mentioned, (M)⁺), FAB+: m/z value in FAB-MS (cation) (unless otherwise mentioned, (M+H)⁺), FAB-: m/z value in FAB-MS (anion) (unless otherwise mentioned, (M-H)⁻), ESI+: m/z value in ESI-MS (cation) (unless otherwise mentioned, (M+H)⁺), ESI-: m/z value in ESI-MS (anion) (unless otherwise mentioned, (M-H)⁻), CI+: m/z value in CI-MS (cation) (unless otherwise mentioned, (M+H)⁺), APCI+: m/z value in APCI-MS (cation) (unless otherwise mentioned, (M+H)⁺), APCI-: m/z value in APCI-MS (anion) (unless otherwise mentioned, (M-H)⁻), NMR1: δ (ppm) of characteristic peak in δ (ppm) by ¹H-NMR in DMSO-d₆, Structure: Structural Formula (a case where HCl, HBr, fum, or TFA is described in the structural formula indicates that the compound is hydrochloride, hydrobromide, fumarate, or trifluoroacetate, respectively. In the case where a numeral is attached before a salt component, the numeral means a molar ratio of the compound to the salt component. For example, a case where 2HCl is described means that the compound is dihydrochloride. Further, a case where H₂O is described in the structural formula indicates that the compound is a hydrate in each case.), Syn: Production Process (the numeral shows that it was prepared using a corresponding starting material, similar to the case of an Example Compound having its number as the Example No.). In the case where P is attached before the numeral, the number shows that it was produced using a corresponding starting material, similar to the case of a Production Example Compound having its number as the Production Example No. A case where a plurality of the numerals is described indicates that the compound was prepared by carrying out the reaction in order starting from the front numeral, using a corresponding starting material. Note: (the racemic mixture means a racemic mixture, the diastereo mixture means a diastereo mixture, and the chiral compound means a chiral compound, in which a part of its stereochemistry is not clear. Further, less polar and more polar mean a low polarity product and a high polarity product, respectively, as compared with the corresponding diastereomers, in thin layer chromatography. Further, 3,4-trans, 1',2'-cis, and the like mean the relative configurations of the substituents or the like. Provided that the numeral which is not dashed means the position substituted in the tetrahydroisoquinolin-1-one ring, and the dashed numeral means the position substituted in the substituent at the 2-position in a tetrahydroisoquinolin-1-one ring. For example, 3,4-trans indicates that the substituents at the 3- and 4-posi-

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tions in the tetrahydroisoquinolin-1-one ring are trans.) Boc: a tert-butoxycarbonyl group, DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene.

In addition,

[Chem. 9]



indicates that the double bond is cis or trans, or a mixture thereof

Production Example 1

10 g of 5-(benzyloxy)-1H-indene-1,2(3H)-dione 2-oxime was added to 20 ml of thionyl chloride at 0° C., followed by stirring for 20 minutes under the same condition. After warming to room temperature, thionyl chloride was evaporated under reduced pressure. To the residue was added 20 ml of a 40% aqueous potassium hydroxide solution, followed by heating under reflux overnight. After cooling to room temperature, and neutralizing by the addition of concentrated hydrochloric acid, the precipitated solid was collected by filtration to obtain 9.9 g of 4-(benzyloxy)-2-(carboxymethyl) benzoic acid as a dark brown powder.

Production Example 2

To a mixture of 2.01 g of diethyl[3-(1,3-dioxolan-2-yl)phenyl]malonate, 2.89 g of calcium chloride, and 50 ml of ethanol was added 2.47 g of sodium borohydride under ice-cooling, followed by stirring at the same temperature for 2 hours and at room temperature for 4 hours. To the reaction solution was added 10 ml of water at room temperature, followed by stirring for 30 minutes. The insoluble material was separated by filtration using Celite, and the filtrate was concentrated under reduced pressure to obtain 0.76 g of 2-[3-(1,3-dioxolan-2-yl)phenyl]propane-1,3-diol as a colorless oily substance.

Production Example 3

A mixture of 1.83 g of 2-[3-(1,3-dioxolan-2-yl)phenyl]propane-1,3-diyl diacetate and 60 ml of a 83% aqueous acetic acid solution was stirred at 50° C. for 2 hours. The reaction solution was concentrated under reduced pressure to obtain 1.59 g of 2-(3-formylphenyl)propane-1,3-diyl diacetate as a colorless oily substance.

Production Example 4

To a solution of 958 mg of (6-methylpyridin-3-yl)methanol, 1.3 ml of triethylamine, and 95 mg of DMAP in 40 ml of dichloromethane was added dropwise 1.08 ml of benzoyl chloride, followed by stirring at room temperature. To the reaction solution was added water, followed by carrying out an extraction operation with chloroform. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 1767 mg of (6-methylpyridin-3-yl)methyl benzoate.

Production Example 5

To a solution of 1767 mg of (6-methylpyridin-3-yl)methyl benzoate in 26.5 ml of chloroform was added 2440 mg of

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m-chloroperbenzoic acid under ice-cooling, followed by stirring for 1 hour. An aqueous potassium carbonate solution was added thereto to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The residue was concentrated under reduced pressure to obtain 1891 mg of (6-methyl-1-oxidopyridin-3-yl)methyl benzoate.

Production Example 6

To a solution of 1891 mg of (6-methyl-1-oxidopyridin-3-yl)methyl benzoate in 38 ml of DMF was added 11 ml of trifluoroacetic anhydride, followed by stirring at room temperature overnight. After evaporating trifluoroacetic anhydride under reduced pressure, a saturated aqueous sodium hydrogen carbonate solution was added thereto, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain 3.675 g of [6-(hydroxymethyl)pyridin-3-yl]methyl benzoate.

Production Example 7

To a solution of 858 mg of pyrazine-2,5-diyl bis(methylene)diacetate in 8.6 ml of methanol was added 600 mg of zeolite, followed by heating under reflux for 4 days. Zeolite was removed by filtration and then concentrated, and the residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain 209 mg of [5-(hydroxymethyl)pyrazine-2-yl]methyl acetate.

Production Example 8

To a mixture of 313 mg of 6-(hydroxymethyl)nicotinamide, 540 mg of triphenylphosphine, 503 mg of N-hydroxyphthalimide, and 4.7 ml of THF was added dropwise 0.53 ml of diisopropyl azodicarboxylate, followed by stirring overnight. After concentration, the solid thus produced was suspended in water, and ethyl acetate was added thereto. After stirring for 30 minutes, the solid was collected by filtration to obtain 292 mg of 6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl}nicotinamide.

Production Example 9

To a suspension of 292 mg of 6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl}nicotinamide in 4.4 ml of methanol was added 0.2 ml of a 40% methyl amine/methanol solution, followed by stirring at room temperature for 1 hour. The reaction solution was concentrated, ethyl acetate was added thereto, and the precipitated crystal was separated by filtration and then concentrated under reduced pressure to obtain 146 mg of 6-[(aminooxy)methyl]nicotinamide.

Production Example 10

To a mixture of 3.0 g of 6-chloronicotinic acid and 111 ml of THF was added 6.4 g of potassium tert-butoxide, followed by heating under reflux for 1 day. The reaction solution was poured into water, neutralized with citric acid, and then extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 2.16 g of 6-tert-butoxynicotinic acid.

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Production Example 11

To a mixed liquid of 2163 mg of 6-tert-butoxynicotinic acid and 32 ml of acetone were added 2297 mg of potassium carbonate and 0.97 ml of methyl iodide, followed by stirring at 35° C. overnight. Ethyl acetate and water were added thereto to carry out liquid separation, and the organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 1.191 g of methyl 6-tert-butoxynicotinate.

Production Example 12

To a mixed liquid of 1191 mg of methyl 6-tert-butoxynicotinate and 35.7 ml of ethanol was slowly added 2153 mg of sodium borohydride, followed by stirring at 50° C. for 18 hours. After the addition of methanol, water and ethyl acetate were added thereto to carry out an extraction operation. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 0.949 g of (6-tert-butoxypyridin-3-yl)methanol.

Production Example 13

To a mixed liquid of 1020 mg of 5-[(aminooxy)methyl]-2-tert-butoxypyridine, which had been obtained by reacting (6-tert-butoxypyridin-3-yl)methanol and N-hydroxyphthalimide in accordance with Production Example 8, and then carrying out the removal of phthalimide in accordance with Production Example 9, and 20 ml of ethyl acetate was added 1.3 ml of concentrated hydrochloric acid under ice-cooling, followed by stirring for 30 minutes. The resulting solid was separated by filtration, concentrated hydrochloric acid was further added to the filtrate, and the precipitated solid was collected by filtration to obtain 351 mg of 5-[(aminooxy)methyl]pyridin-2(1H)-one hydrochloride as a colorless solid.

Production Example 14

To a mixture of 659 mg of 1-(chloromethyl)-4-(methylsulfonyl)benzene and 10 ml of DMSO were added 525 mg of N-hydroxyphthalimide and 445 mg of potassium carbonate, followed by stirring at 50° C. for 2 hours. The reaction solution was cooled, water was then added thereto, and the precipitated crystal was collected by filtration to obtain 685 mg of 2-{[4-(methylsulfonyl)benzyl]oxy}-1H-isindole-1,3(2H)-dione as a white solid.

Production Example 15

To a solution of 5.08 g of tert-butyl[4-(hydroxymethyl)phenoxy]acetate and 4.6 ml of triethylamine in 30 ml of dichloromethane was added 1.98 ml of methanesulfonyl chloride under ice-cooling, followed by stirring for 1 hour under ice-cooling. The reaction solution was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was then evaporated. To a solution of the obtained residue in 40 ml of DMF was added 4.26 g of sodium azide, followed by stirring at 60° C. for 15 hours. After leaving it to be cooled, the reaction solution was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was then evaporated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate-

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hexane) to obtain 5.16 g of tert-butyl[3-(azidomethyl)phenoxy]acetate as a pale yellow oily substance.

Production Example 16

To a mixed liquid of 5.00 g of methyl 5-formylthiophene-3-carboxylate and 50 ml of THF was added 0.67 g of sodium borohydride under ice-cooling. To the reaction solution was added dropwise 5 ml of methanol, followed by stirring for 1 hour under ice-cooling. The reaction solution was added with 1 M hydrochloric acid, extracted with ethyl acetate, and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was then evaporated to obtain 4.86 g of methyl 5-(hydroxymethyl)thiophene-3-carboxylate as a pale yellow oily substance.

Production Example 17

To a mixed liquid of 4.86 g of methyl 5-(hydroxymethyl)thiophene-3-carboxylate and 50 ml of dichloromethane was added 4.12 ml of thionyl chloride under ice-cooling, followed by stirring at room temperature for 15 hours. The reaction solution was concentrated, added with ethyl acetate, and then washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was then evaporated to obtain 4.90 g of methyl 5-(chloromethyl)thiophene-3-carboxylate as a pale yellow oily substance.

Production Example 18

To a solution of 3.69 g of di-tert-butyl imidodicarbonate in 54 ml of DMF was added 1.91 g of potassium tert-butoxide at 0° C. under argon, followed by stirring at room temperature for 1 hour. A solution of 2.7 g of methyl 5-(chloromethyl)thiophene-3-carboxylate in 8.1 ml of DMF was slowly added thereto, followed by stirring at room temperature overnight. Water and ethyl acetate were added to the reaction solution, followed by carrying out an extraction operation, and the organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 4.394 g of methyl 5-[[bis(tert-butoxycarbonyl)amino]methyl]thiophene-3-carboxylate.

Production Example 19

To a mixed liquid of 400 mg of ethyl difluoro(3-methylphenyl) acetate and 10 ml of carbon tetrachloride were added 349 mg of N-bromosuccinimide and 15 mg of 2,2'-azobis(isobutyronitrile), followed by heating under reflux for 2 hours. After cooling the reaction solution, the insoluble material was separated by filtration, and the filtrate was concentrated. The residue was added with hexane, washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. After evaporating the solvent, the residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 458 mg of ethyl[3-(bromomethyl)phenyl](difluoro) acetate as a colorless oily substance.

Production Example 20

To a mixed liquid of 2.89 g of ethyl 2-methyl-2-(3-methylphenyl)propionate and 90 ml of carbon tetrachloride were

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added 4.98 g of N-bromosuccinimide and 115 mg of 2,2'-azobis(isobutyronitrile), followed by stirring at 80° C. for 2 hours, and 4.98 g of N-bromosuccinimide and 115 mg of 2,2'-azobis(isobutyronitrile) were further added thereto, followed by stirring at 80° C. for 14 hours. After cooling the reaction solution, the insoluble material was separated by filtration, and the solvent was evaporated. To the residue was added hexane and followed by washing with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was then evaporated to obtain 6.0 g of a pale yellow oily substance. The obtained oily substance was dissolved in 30 ml of THF, and 21.7 ml of diethyl phosphite and 29.3 ml of diisopropylethylamine were added thereto under ice-cooling, followed by stirring at room temperature for 13 hours. The reaction solution was poured into ice water, followed by extraction with hexane. The organic layer was washed with 1 M hydrochloric acid and a saturated aqueous sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 2.95 g of ethyl 2-[3-(dibromomethyl)phenyl]-2-methylpropionate as a pale yellow oily substance.

Production Example 21

To a mixed liquid of 2.95 g of ethyl 2-[3-(dibromomethyl)phenyl]-2-methylpropionate and 30 ml of acetic acid was added 4.77 g of potassium acetate, followed by stirring at 100° C. for 6 hours. After cooling the reaction solution, 10 ml of 6 M hydrochloric acid was added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was poured into water, followed by extraction with hexane, and the organic layer was washed with water and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was then evaporated to obtain 1.74 g of ethyl 2-(3-formylphenyl)-2-methylpropionate as a colorless oily substance.

Production Example 22

To a mixed liquid of 1.00 g of tert-butyl piperidin-4-ylcarbamate and 20 ml of pyridine was added 0.77 ml of methane-sulfonyl chloride, followed by stirring at room temperature for 18 hours. After evaporating the pyridine under reduced pressure, ethyl acetate was added thereto, followed by washing with a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution, and a saturated aqueous sodium chloride solution. After drying the organic layer over anhydrous magnesium sulfate, the solvent was evaporated, and the obtained solid was washed with diethyl ether to obtain 1.19 g of t-butyl[1-(methylsulfonyl)piperidin-4-yl]carbamate as a white solid.

Production Example 23

To a solution of 1 g of tert-butyl[3-(cyanomethyl)phenoxy]acetate in 20 ml of THF and 10 ml of methanol was added dropwise a suspension of 1.31 g of cobalt chloride and 20 ml of water, and then 459 mg of sodium borohydride was portionwise added thereto at room temperature. After stirring at room temperature for 10 minutes, the insoluble material was separated by filtration over Celite, washed with methanol, and then concentrated. The obtained residue was extracted with chloroform, and dried over anhydrous magnesium sulfate, and the solvent was then evaporated. The obtained residue

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was purified by silica gel column chromatography (eluent: chloroform-methanol-saturated aqueous ammonia) to obtain 632 mg of tert-butyl[3-(2-aminoethyl)phenoxy]acetate as a pale yellow oily substance.

Production Example 24

To a mixed liquid of 5.16 g of t-butyl[3-(azidomethyl)phenoxy]acetate and 50 ml of THF were added 6.17 g of triphenylphosphine and 1.04 ml of water, followed by stirring at room temperature for 4 days. The solvent was evaporated and diisopropyl ether was added thereto. The precipitated solid was separated by filtration and the solvent was evaporated again. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol-saturated aqueous ammonia) to obtain 4.10 g of t-butyl[3-(aminomethyl)phenoxy]acetate as a pale yellow oily substance.

Production Example 25

To a mixed liquid of 2.00 g of (1RS,2SR)-2-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylic acid and 40 ml of dichloromethane were added 1.41 ml of 2-(trimethylsilyl)ethanol, 0.40 g of DMAP, and 2.21 g of WSC in this order, followed by stirring at room temperature for 60 hours. After evaporating the solvent, ethyl acetate was added thereto, followed by washing with water, a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution, and a saturated aqueous sodium chloride solution in this order. The organic layer was dried over anhydrous magnesium sulfate and the solvent was then evaporated to obtain 2.82 g of 2-(trimethylsilyl)ethyl(1RS,2SR)-2-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate as a colorless oily substance.

Production Example 26

To a solution of 2.82 g of 2-(trimethylsilyl)ethyl(1RS,2SR)-2-[(tert-butoxycarbonyl)amino]cyclohexanecarboxylate in 10 ml of ethyl acetate, were added 20 ml of 4 M hydrogen chloride/ethyl acetate under ice-cooling, followed by stirring at room temperature for 6 hours. The reaction solution was evaporated to obtain 2.30 g of 2-(trimethylsilyl)ethyl(1RS,2SR)-2-aminocyclohexanecarboxylate as a colorless amorphous substance.

Production Example 27

To a mixed liquid of 4.40 g of N-[(benzyloxy)carbonyl]-3-[(methylsulfonyl)amino]-D-alanine methyl ester, 100 ml of THF, and 50 ml of ethanol was added 1.13 g of lithium chloride, and 1.01 g of sodium borohydride was further added thereto under ice-cooling. The reaction solution was stirred at room temperature for 14 hours, and the solvent was then evaporated under reduced pressure. After adding 150 ml of water, concentrated hydrochloric acid was added thereto until the pH reached 2 to 3. The solution was extracted with ethyl acetate, washed with a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was evaporated to obtain 3.10 g of benzyl[(1R)-2-hydroxy-1-[[[(methylsulfonyl)amino]methyl]ethyl]carbamate as a white solid.

Production Example 28

To a mixed liquid of 3.10 g of benzyl[(1R)-2-hydroxy-1-[[[(methylsulfonyl)amino]methyl]ethyl]carbamate and 50 ml

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of ethanol was added 500 mg of 5% palladium/carbon, followed by stirring at room temperature for 2 hours under a hydrogen atmosphere. The palladium/carbon was separated by filtration and the solvent was then evaporated to obtain 1.72 g of N-[(2R)-2-amino-3-hydroxypropyl]methanesulfonamide as a colorless oily substance.

Production Example 29

To 700 mg of 2-(6-methoxypyridin-2-yl)ethylamine was added 10 ml of a 47% aqueous hydrogen bromide solution, followed by stirring at 80° C. for 60 hours. After evaporating the solvent, the residue was washed with diethyl ether to obtain 1.21 g of a 6-(2-aminoethyl)pyridin-2(1H)-one hydrobromide as a pale brown solid.

Production Example 30

A mixture of 3980 mg of 2-[2-(1H-tetrazol-1-yl)ethyl]-1H-isoindole-1,3(2H)-dione, 0.90 g of hydrazine monohydrate, and 80 ml of ethanol was stirred at 70° C. for 12 hours.

The reaction solution was left to be cooled and the insoluble material was then collected by filtration. The filtered material was suspended in dioxane and 3.57 g of di-tert-butyl dicarbonate was added thereto at room temperature, followed by stirring for 12 hours. The insoluble material was separated by filtration and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using hexane/ethyl acetate as an eluent solvent to obtain 2210 mg of tert-butyl[2-(1H-tetrazol-1-yl)ethyl]carbamate as a colorless solid.

Production Example 31

To a solution of 2.62 g of tert-butyl 1H-pyrrole-3-carboxylate and 7.96 g of N-(2-bromoethyl)phthalimide in DMF (100 ml) was added 10.2 g of cesium carbonate at room temperature, followed by stirring for 12 hours. The reaction solution was diluted with water and extracted with ethyl acetate. The extract was washed with saturated brine and then dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography using hexane/chloroform as an eluent solvent, and washed with diethyl ether to obtain 670 mg of tert-butyl 1-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1H-pyrrole-3-carboxylate as a colorless solid.

Production Example 32

A mixture of 660 mg of tert-butyl 1-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1H-pyrrole-3-carboxylate, 194 mg of hydrazine monohydrate, and 19 ml of ethanol was stirred at 70° C. for 12 hours. The reaction solution was left to be cooled and the insoluble material was then separated by filtration. The filtrate was concentrated under reduced pressure to obtain 430 mg of tert-butyl 1-(2-aminoethyl)-1H-pyrrole-3-carboxylate as a yellow oily substance.

Production Example 33

To a solution of 8.75 g of 2,4-dichlorobenzaldehyde in 100 ml of chloroform were added 5.11 g of cyclopentylamine and 5 g of Molecular Sieves 4A, followed by stirring at room temperature overnight. After removing the Molecular Sieves 4A by filtration, 6.48 g of homophthalic anhydride was added thereto, followed by stirring at room temperature overnight

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and then reflux for 5 hours. After concentrating under reduced pressure, ethyl acetate and a 1 M aqueous sodium hydroxide solution were added thereto to carry out a liquid separation operation. The aqueous layer was acidified by the addition of 1 M hydrochloric acid, followed by extraction with chloroform-isopropyl alcohol (3:1). The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was then evaporated under reduced pressure. The obtained residue was added with ether and collected by filtration to obtain 4.48 g of 3,4-cis-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (Production Example 33-1) as a colorless crystal. The mother liquid was concentrated to obtain 6.46 g of 3,4-trans-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (Production Example 33-2) as a colorless amorphous substance.

Production Example 34

To a mixed solution of 2,4-dichlorobenzaldehyde in chloroform-methanol were added trans-2-aminocyclohexanol, triethylamine, and anhydrous sodium sulfate at room temperature, the reaction solution was stirred at 50° C. overnight, and homophthalic anhydride was then added thereto at room temperature, followed by stirring at room temperature overnight. After removing sodium sulfate by filtration, chloroform and a 1 M aqueous sodium hydroxide solution were added thereto to carry out a liquid separation operation, and the aqueous layer was stirred at room temperature for 2 hours. It was acidified by the addition of 1 M hydrochloric acid, and ethyl acetate was added thereto to carry out a liquid separation operation. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. To the residue was added diethyl ether, followed by stirring at room temperature overnight. The precipitated crystal was collected by filtration to obtain 7655 mg of 3RS,4RS-3-(2,4-dichlorophenyl)-2-(1SR,2SR-2-hydroxycyclohexyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (Production Example 34-1) as a colorless crystal. After concentrating the mother liquid, the residue was purified by silica gel column chromatography (eluent:chloroform:methanol) to obtain 6600 mg of 3SR,4SR-3-(2,4-dichlorophenyl)-2-(1RS,2RS-2-hydroxycyclohexyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (Production Example 34-2) as a colorless crystal.

Production Example 35

To 4.33 g of (3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid were added 50 ml of ethanol and 2 ml of concentrated sulfuric acid, followed by heating under reflux overnight. Ethyl acetate and water were added thereto to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 2.3 g of ethyl[(3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate as a yellow foam.

Production Example 36

To a solution of 2.25 g of ethyl(3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-

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tetrahydroisoquinoline-4-carboxylate in 30 ml of acetonitrile were added 0.75 ml of methanesulfonyl chloride and 1.6 ml of diisopropylethylamine, followed by stirring at room temperature overnight. Ethyl acetate and water were added thereto to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The residue was added with diethyl ether for crystallization, and collected by filtration to obtain 2.02 g of ethyl(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate as a colorless crystal.

Production Example 37

To a solution of 1.4 g of ethyl(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate in 20 ml of DMF was added 229 mg of sodium hydride under ice-cooling, followed by stirring at the same temperature for 10 minutes, and then 0.17 ml of methyl iodide was added thereto, followed by stirring under ice-cooling for 30 minutes. Water was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain 545 mg of ethyl(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methyl(methylsulfonyl)amino)cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate as a colorless amorphous substance.

Production Example 38

To a mixture of 2.0 g of ethyl(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate, 10 ml of methanol, and 10 ml of THF was added 10 ml of a 1 M aqueous sodium hydroxide solution, followed by stirring at room temperature for 1 hour. The solution was acidified by the addition of 1 M hydrochloric acid, and then extracted with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure to obtain 1.9 g of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid as a pale yellow crystal.

Production Example 39

A mixture of 8 g of 4-(benzyloxy)-2-(carboxymethyl)benzoic acid and 30 ml of acetyl chloride was heated under reflux for 3 hours. The reaction solution was concentrated under reduced pressure, added with ether, and collected by filtration to obtain 7.50 g of 6-(benzyloxy)-1H-isochromene-1,3(4H)-dione as a dark brown solid.

Production Example 40

To 612 mg of 6-[(aminooxy)methyl]pyridin-2(1H)-one, which had been prepared by subjecting 2-[(6-oxo-1,6-dihydropyridin-2-yl)methoxy]-1H-isoindole-1,3(2H)dione to removal of phthalimide in accordance with Production Example 9, was added 1.6 ml of a 4 M hydrogen chloride/

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ethyl acetate solution, and the precipitated solid was collected by filtration to obtain 263 mg of 6-[(aminooxy)methyl]pyridin-2(1H)-one hydrochloride as a colorless solid.

Production Example 41

To 2.04 g of (4-methyl-1H-imidazol-5-yl)methanol hydrochloride was added 20 ml of acetonitrile, and 2.1 ml of triethylamine, 3.14 g of di-tert-butyl dicarbonate, and 0.17 g of DMAP were added thereto under ice-cooling, followed by stirring at room temperature. After concentrating the reaction solution under reduced pressure, ethyl acetate and water were added thereto to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The obtained residue was reacted with N-hydroxyphthalimide in accordance with Production Example 14, reacted with methylamine in accordance with Production Example 9, and then subjected to deprotection of a Boc group in accordance with Production Example 26 to obtain 0.53 g of 5-[(aminooxy)methyl]-4-methyl-1H-imidazole dihydrochloride as a colorless solid.

Production Example 42

To a solution of 529 mg of (5-fluoropyridin-2-yl)methanol and 0.64 ml of triethylamine in 8 ml of dichloromethane was added 0.35 ml of methanesulfonyl chloride under ice-cooling, followed by stirring for 1 hour under ice-cooling. The reaction solution was poured into water, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate, and the solvent was then evaporated. The obtained residue was reacted with N-hydroxyphthalimide in accordance with Production Example 14 to obtain 522 mg of 2-[(5-fluoropyridin-2-yl)methoxy]-1H-isoindole-1,3(2H)-dione as a white solid.

Production Example 43

To a mixture of 2.97 g of 4-(hydroxymethyl)phenol, 4.90 g of tert-butyl bromoacetate, and 25 ml of DMF was added 4.96 g of potassium carbonate at room temperature, followed by stirring for 12 hours. To the reaction solution was added water, followed by extraction with ethyl acetate. The organic layer was washed with water and saturated brine, and dried over anhydrous magnesium sulfate, and the solvent was then evaporated. The residue was purified by silica gel column chromatography (eluent: ethyl acetate-hexane) to obtain a pale yellow oily substance. This oily substance was subjected to methanesulfonylation in accordance with Production Example 15, and then reacted with sodium azide to obtain 4.03 g of tert-butyl[4-(azidomethyl)phenoxy]acetate as a pale yellow oily substance.

Production Example 44

To a solution of 1.63 g of ethyl(3RS,4RS)-2-[(1SR,2SR)-2-[(3-chloropropyl)sulfonyl]amino]cyclohexyl]-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylate in 20 ml of THF was added 142 mg of sodium hydride, followed by stirring at 50° C. overnight. Ethyl acetate and water were added thereto to carry out a liquid separation operation. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated under reduced

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pressure. The residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 466 mg of ethyl(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-(1,1-dioxidoisothiazolidin-2-yl)cyclohexyl]-1-oxo-tetrahydroisquinoline-4-carboxylate as a colorless crystal.

Production Example 45

A solution of 5.0 g of 4-bromothiophene-2-carbaldehyde, 11.4 ml of vinyltributyltin, and 3.6 g of tetrakis(triphenylphosphine) palladium in 100 ml of toluene was heated at 110° C. for 4 hours under a sealed tube condition. The organic layer was extracted with ethyl acetate and washed with water. In addition, the organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 3.4 g of 4-vinylthiophene-2-carbaldehyde as a brown liquid.

Production Example 46

A solution of 5 g of methyl 1-methyl-1H-imidazole-5-carboxylate and 22.5 g of paraformaldehyde in 50 ml of methanol was heated at 140° C. for 60 hours under a sealed tube condition. The precipitate was removed by filtration and the solution was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain 4 g of methyl 2-(hydroxymethyl)-1-methyl-1H-imidazole-5-carboxylate as a white solid.

Production Example 47

7.4 ml of phosphorous oxychloride was added dropwise to 8.1 ml of DMF at 0° C., followed by warming to room temperature. To the solution was added ethyl 3-furnate, followed by warming to 126° C. and stirring for 1 hour. After cooling to room temperature, the reaction solution was poured into ice water. The organic layer was extracted with diethyl ether and washed with a saturated aqueous sodium carbonate solution. In addition, the organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 850 mg of ethyl 5-formyl-3-furnate as a yellow solid.

Production Example 48

To a mixed liquid of 1.51 g of potassium cyanide and 70 ml of acetonitrile, 6.12 g of 1,4,7,10,13,16-hexaoxacyclooctadecane was added, followed by stirring for 2 hours. Thereafter, a solution of 5.00 g of tert-butyl 3-(chloromethyl)benzoate in 30 ml of acetonitrile was added thereto, followed by stirring at room temperature for 18 hours. The reaction solution was concentrated, diluted with diethyl ether-hexane (1:1), and then washed with water and a saturated aqueous sodium chloride solution. After drying over anhydrous magnesium sulfate, the solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 3.86 g of tert-butyl 3-(cyanomethyl)benzoate as a colorless oily substance.

Production Example 49

A solution of 2 g of (benzyloxy)acetic acid in 30 ml of DMF was cooled to 0° C., and 2.44 g of 1-(4-aminophenyl)ethanone, 294 mg of DMAP, and 3.73 g of WSC/hydrochloric

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ride were added thereto, followed by stirring at room temperature for 3 hours. Liquid separation was carried out with ethyl acetate-1 M hydrochloric acid. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure to obtain 3.12 g of N-(4-acetylphenyl)-2-(benzyloxy)acetamide.

Production Example 50

To a solution of 1.64 g of ethyl 2-(hydroxymethyl)isonicotinate in 32.8 ml of dichloromethane were added 1.24 ml of dihydropyran and 2.32 g of pyridinium p-toluenesulfonate, followed by stirring overnight. Ethyl acetate was added thereto, followed by washing with a saturated aqueous ammonium chloride solution and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 2.4 g of ethyl 2-[(tetrahydro-2H-pyran-2-yl)oxy)methyl]isonicotinate.

Production Example 51

To a solution of 1.8 g of 1-[6-(hydroxymethyl)pyridin-2-yl]ethanone oxime in 36 ml of methanol was added 500 mg of 10% palladium-carbon (50% wet) under an argon atmosphere, followed by stirring for 7 hours under a hydrogen atmosphere. After filtration through Celite, the filtrate was evaporated under reduced pressure to obtain 1.5 g of [6-(1-aminoethyl)pyridin-2-yl]methanol.

Production Example 52

To a solution of 2.06 g of 3-amino-4-hydroxybenzoic acid in 20.6 ml of THF was added 4.81 g of CDI, followed by stirring at room temperature for 1 hour. The reaction mixture was added dropwise to a mixed liquid of 3.06 g of sodium borohydride in 20.6 ml of THF and 8.26 ml of water, cooled to 0° C., which had been separately prepared, followed by stirring overnight. 1 M hydrochloric acid was added thereto, followed by extracting with ethyl acetate, and washing with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 1.2 g of 5-(hydroxymethyl)-1,3-benzoxazol-2(3H)-one.

Production Example 53

To 5 g of diethylpyridine-2,4-dicarboxylate were added 50 ml of ethanol and 50 ml of dichloroethane, followed by ice-cooling. 932 mg of sodium borohydride was added portionwise thereto, followed by stirring for 1 hour under ice-cooling, and further at room temperature for 15 hours. After ice-cooling the reaction solution, 5 ml of 6 M hydrochloric acid was added thereto, followed by stirring for 5 minutes and concentrating. A saturated aqueous sodium hydrogen carbonate solution was added thereto, followed by extracting with chloroform-isopropanol (10:1) and drying over anhydrous magnesium sulfate. After concentrating under reduced pressure, the residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain 0.7 g of ethyl 4-(hydroxymethyl)pyridine-2-carboxylate (Production Example 53-1) and 1.6 g of ethyl 2-(hydroxymethyl)isonicotinate (Production Example 53-2), respectively.

Production Example 54

To 1.6 g of 1-(6-methoxypyridin-2-yl)ethanamine was added 23.7 ml of a 47% aqueous hydrobromic acid solution,

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followed by stirring at 80° C. for 60 hours. After evaporating the solvent under reduced pressure, the residue was washed with diethyl ether to obtain 2.95 g of 6-(1-aminoethyl)pyridin-2(1H)-one hydrobromide as a pale brown solid.

Production Example 55

To a solution of 2.31 g of tert-butyl 1H-pyrazole-3-carboxylate and 6.98 g of N-(2-bromoethyl)phthalimide in DMF (65 mL) was added 8.95 g of cesium carbonate at room temperature, followed by stirring for 12 hours. The reaction solution was diluted with water, followed by extraction with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: chloroform-hexane) to obtain 1.51 g of tert-butyl 1-[2-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)ethyl]-1H-pyrazole-3-carboxylate as a colorless solid.

Production Example 56

To a mixture of 2.92 g of (2-hydroxyphenyl)acetonitrile, 4.71 g of tert-butyl bromoacetate and 110 mL of DMF was added 6.06 g of potassium carbonate at room temperature, followed by stirring for 12 hours. To the reaction solution was added water, followed by extraction with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography using hexane/ethyl acetate as an eluent solvent to obtain 5.29 g of tert-butyl[2-(cyanomethyl)phenoxy]acetate as a yellow oily substance.

Production Example 57

A mixture of 1.38 g of 6-(hydroxymethyl)pyridin-2(1H)-one, 2.15 g of tert-butyl bromoacetate, 3.07 g of silver oxide, and 33 mL of DMF was stirred at room temperature for 12 hours, and then at 60° C. for 12 hours. The insoluble material was separated by filtration and the filtrate was concentrated under reduced pressure. The residue was diluted with ethyl acetate, followed by washing with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 1.92 g of tert-butyl {[6-(hydroxymethyl)pyridin-2-yl]oxy}acetate as a yellow oily substance.

Production Example 58

To a mixture of 1.00 g of 3-hydroxybenzaldehyde, 1.80 g of tert-butyl(R)-lactate, 2.58 g of triphenylphosphine, and 40 mL of THF was added 1.71 g of diethyl azodicarboxylate at room temperature, followed by stirring for 12 hours. The reaction solution was diluted with ethyl acetate, followed by washing with a 5% aqueous sodium hydrogen carbonate solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 1.49 g of tert-butyl(2S)-2-(3-formylphenoxy)propanoate as a colorless oily substance.

To a solution of 1.48 g of tert-butyl(2S)-2-(3-formylphenoxy)propanoate in methanol (30 mL) was added 0.48 g of sodium borohydride under ice-cooling, followed by stirring for 1 hour. The reaction solution was diluted with ethyl acetate, added with water, neutralized with 1 M hydrochloric

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acid, and extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 1.38 g of tert-butyl(2S)-2-[3-(hydroxymethyl)phenoxy]propanoate as a colorless oily substance.

Production Example 59

A solution of 2.90 g of 1,3-phenylene diacetic acid, 3.00 g of 4-methoxybenzylbromide, and 2.99 g of potassium hydrogen carbonate in 15 mL of DMF was stirred at room temperature for 36 hours. To the reaction solution was added water, followed by neutralization with 1 M hydrochloric acid. The product was extracted with ethyl acetate and the organic layer was dried over anhydrous magnesium sulfate. After concentrating under reduced pressure, 4.72 g of a colorless oily substance was obtained. A mixture of the obtained colorless oily substance (4.72 g), 2.42 g of HOBt, 2.78 g of WSC hydrochloride, 3.99 g of ammonium chloride, 7.55 g of triethylamine, and 18 mL of DMF was stirred at room temperature for 12 hours. The reaction solution was diluted with water and extracted with ethyl acetate. The organic layer was washed with saturated brine and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 4-methoxybenzyl[3-(2-amino-2-oxoethyl)phenyl]acetate as a colorless solid.

To a solution of 1.31 g of 4-methoxybenzyl[3-(2-amino-2-oxoethyl)phenyl]acetate in pyridine (20 mL) was added 718 mg of methanesulfonyl chloride under ice-cooling, followed by stirring for 2 hours. The reaction solution was concentrated under reduced pressure. The residue was diluted with ethyl acetate and washed with a 5% aqueous citric acid solution, a saturated aqueous sodium hydrogen carbonate solution, and then a saturated aqueous sodium chloride solution in this order. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 1.25 g of 4-methoxybenzyl[3-(cyanomethyl)phenyl]acetate as a yellow oily substance.

Production Example 60

A mixture of 5.05 g of 5-methyl-2-furanecarboxylic acid, 7.14 g of CDI, and 40 mL of DMF was stirred at 50° C. for 2 hours. To the reaction solution were added 6.71 g of DBU and 6.53 g of 2-methyl-2-propanol at room temperature, followed by stirring at 50° C. for 48 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was diluted with diethyl ether and washed with a 5% aqueous ammonium chloride solution, a saturated aqueous sodium hydrogen carbonate solution, and then a saturated aqueous sodium chloride solution in this order. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexane-ethyl acetate) to obtain 2.82 g of tert-butyl 5-methyl-2-furanecarboxylate as a yellow oily substance.

Production Example 61

To a solution of 1643 mg of 1-[6-(hydroxymethyl)pyridin-2-yl]ethanone in 25 mL of ethanol was added 0.72 mL of a 50% aqueous hydroxylamine solution, followed by stirring overnight. The reaction solution was concentrated under reduced

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pressure to obtain 1806 mg of 1-[6-(hydroxymethyl)pyridin-2-yl]ethanone oxime as an amorphous substance.

Production Example 62

To a mixture of 2.06 g of tert-butyl({6-[(hydroxymethyl)pyridin-2-yl]oxy}acetate, 2.60 g of triphenylphosphine, 2.70 g of phthalimide, and 40 mL of THF was added 1.73 g of diethyl azodicarboxylate at room temperature, followed by stirring for 36 hours. To the reaction solution was added ethyl acetate, followed by washing with a 5% aqueous sodium hydrogen carbonate solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure, and the residue was purified by silica gel column chromatography to obtain 2.33 g of ({6-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)methyl]pyridin-2-yl}oxy)acetic acid as a colorless solid.

Production Example 63

To a mixture of 1266 mg of {2-[(tetrahydro-2H-pyran-2-yloxy)methyl]pyridin-4-yl}methyl benzoate and 25 ml of methanol was added 1166 mg of pyridinium p-toluenesulfonate, followed by stirring for 2 hours. A saturated aqueous sodium hydrogen carbonate solution and chloroform were added thereto for extraction, and the organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain 941 mg of [2-(hydroxymethyl)pyridin-4-yl]methyl benzoate as an amorphous substance.

Production Example Compounds 64 to 371 were prepared in the same manner as the methods of Production Examples 1 to 63 and the methods of Examples to be described later, using each of the corresponding starting materials. The structures and the physicochemical data of Production Example Compounds are shown in Tables 14 to 69.

Example 1

To a solution of 808 mg of 3,4-cis-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid, 0.3 ml of phenylethylamine, and 405 mg of HOBt in dichloromethane (20 ml) was added 576 mg of WSC hydrochloride at room temperature, followed by stirring for 2 hours. To the reaction solution was added chloroform, and the organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent:chloroform) to obtain 902 mg of 3,4-trans-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-N-phenylethyl-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 2

To a mixture of 202 mg of 3,4-cis-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid and 5 ml of dichloromethane were added 0.055 ml of oxalyl chloride and one drop of DMF under ice-cooling, followed by stirring at room temperature for 30 minutes. The reaction solution was concentrated under reduced pressure, and the obtained residue was dissolved in 5 ml of THF, and 0.13 ml of phenylethylamine and 0.07 ml of triethylamine were added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, added with ethyl

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acetate, and washed with water and a saturated aqueous sodium chloride solution in this order. The organic layer was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent:chloroform), and the obtained crude product was then collected by filtration using diethyl ether to obtain 127 mg of 3,4-cis-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-N-phenylethyl-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 3

To a mixture of 254 mg of 3,4-trans-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-N-[2-(2-pyridinyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 5 ml of dichloromethane was added 173 mg of m-chloroperbenzoic acid under ice-cooling, followed by stirring at room temperature overnight. To the reaction solution was added chloroform, washed with a 10% aqueous sodium hydrogen sulfite solution and a saturated aqueous sodium chloride solution in this order, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent; chloroform-methanol) and then recrystallized from ethanol to obtain 138 mg of 3,4-trans-2-cyclopentyl-3-(2,4-dichlorophenyl)-N-[2-(1-oxidopyridin-2-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 4

To 654 mg of N-[(3,4-trans-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]-β-alanine ethyl ester were added 5 ml of THF, 2 ml of methanol, and 5 ml of a 1 M aqueous sodium hydroxide solution at room temperature, followed by stirring at 50° C. for 3 hours. After neutralization by the addition of 1 M hydrochloric acid, ethyl acetate was added for extraction. The organic layer was washed with water and a saturated aqueous sodium chloride solution in this order, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The obtained white solid was recrystallized from ethyl acetate to obtain 294 mg of N-[(3,4-trans-2-cyclopentyl-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]-β-alanine as a colorless powdered crystal.

Example 5

To 410 mg of tert-butyl {2-[3-(2,4-dichlorophenyl)-1-oxo-4-[(2-phenylethyl)carbamoyl]-3,4-dihydroisoquinolin-2-(1H)-yl]ethyl}carbamate was added 4 ml of a 4 M hydrogen chloride/ethyl acetate solution, followed by stirring at room temperature for 2 hours. The solvent was evaporated under reduced pressure, and chloroform and a 1 M aqueous sodium hydroxide solution were then added to carry out a liquid separation operation. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The obtained residue was recrystallized from ethyl acetate-hexane to obtain 192 mg of 2-(2-aminoethyl)-3-(2,4-dichlorophenyl)-1-oxo-N-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless powdered crystal.

Example 6

To a solution of 537 mg of 3,4-trans-2-(trans-4-aminocyclohexyl)-3-(2,4-dichlorophenyl)-1-oxo-N-(2-phenylethyl)-

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1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 10 ml of dichloromethane were added 0.33 ml of an aqueous formalin solution and 893 mg of sodium triacetoxymethylborohydride, followed by stirring at room temperature overnight. To the reaction solution was added a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with chloroform. The organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous sodium sulfate, and the solvent was evaporated. The obtained residue was purified by silica gel column chromatography (eluent: chloroform-methanol), and the obtained white solid was recrystallized from ethyl acetate to obtain 82 mg of 3,4-trans-3-(2,4-dichlorophenyl)-2-[trans-4-(dimethylamino)cyclohexyl]-1-oxo-N-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 7

To a solution of 2.03 g of 3,4-trans-2-cyclopentyl-1-oxo-4-[(2-phenylethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid in 20 ml of THF was added 810 mg of CDI, followed by stirring under heating at 50° C. for 1 hour. After cooling to room temperature, a mixture of 200 mg of sodium borohydride and 10 ml of water was added thereto, followed by stirring at room temperature for 4 hours. Ethyl acetate and water were added thereto to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium chloride solution, dried over sodium sulfate, and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform), and the obtained solid was recrystallized from ethyl acetate to obtain 255 mg of 3,4-trans-2-cyclopentyl-3-(hydroxymethyl)-1-oxo-N-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 8

To 304 mg of (3RS,4RS)-N-(benzyloxy)-3-(4-methyl-3-nitrophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide were added 10 ml of acetic acid and 560 mg of reduced iron, followed by stirring at 50° C. overnight. To the reaction solution was added methanol, followed by filtration through Celite, and after concentrating the mother liquid, ethyl acetate and water were added thereto to carry out a liquid separation operation. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform:methanol). The obtained solid was made into hydrochloride using a 4 M hydrogen chloride/ethyl acetate solution, and recrystallized from isopropyl alcohol to obtain 180 mg of (3RS,4RS)-3-(3-amino-4-methylphenyl)-N-(benzyloxy)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide hydrochloride as a pale yellow powdered crystal.

Example 9

To 393 mg of 3,4-trans-2-cyclopentyl-3-(hydroxymethyl)-1-oxo-N-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide were added 10 ml of THF and 44 mg of sodium hydride, followed by stirring at room temperature for 30 minutes. To the reaction mixture was added 161 mg of 4-chlorobenzylbromide, followed by stirring at room temperature

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overnight. To the reaction mixture were added ethyl acetate and water to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform) and the obtained solid was crystallized from ether-hexane, and collected by filtration to obtain 134 mg of 3,4-trans-3-[(4-chlorobenzyl)oxy]methyl-2-cyclopentyl-1-oxo-N-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless powdered crystal.

Example 10

To a solution of 573 mg of (3RS,4RS)-N-(2-chloroethyl)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 10 ml of DMF were added 150 mg of sodium iodide and 340 mg of 1H-pyrazole, followed by stirring at 100° C. for 24 hours. Ethyl acetate and water were added thereto to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain a colorless crystal. The crystal was recrystallized from ethanol to obtain 176 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-[2-(1H-pyrazol-1-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless powdered crystal.

Example 11

To a mixture of 270 mg of (3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-3-(2,4-dichlorophenyl)-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 5 ml of pyridine was added 0.11 ml of acetic anhydride, followed by stirring at room temperature for 2 hours. Ethyl acetate and water were added thereto to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure.

The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain a colorless crystal. The obtained crystal was added with diethyl ether and collected by filtration to obtain 55 mg of (3RS,4RS)-2-[(1SR,2SR)-2-acetamidocyclohexyl]-3-(2,4-dichlorophenyl)-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless powdered crystal.

Example 12

To a mixture of 538 mg of (3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-N-(benzyloxy)-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 2.5 ml of pyridine was added 0.15 ml of methanesulfonyl chloride, followed by stirring at room temperature for 6 hours. Ethyl acetate and water were added thereto to carry out a liquid separation operation, and the organic layer was washed with a 1 M aqueous hydrochloric acid solution and a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform) and then recrystallized from

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ethyl acetate-hexane to obtain 206 mg of (3RS,4RS)-N-(benzyloxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless powdered crystal.

Example 13

To a mixed liquid of 200 mg of (3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-N-enzyloxy)-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 40 ml of dimethoxyethane was added 357 mg of sulfamide, followed by stirring at 80° C. for 2 days. The reaction solution was concentrated, added with chloroform, and then washed with water. The organic layer was dried over anhydrous magnesium sulfate, and the solvent was then evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol), crystallized from ethyl acetate, and collected by filtration to obtain 62 mg of (3RS,4RS)-2-[(1SR,2SR)-2-[(aminosulfonyl)amino]cyclohexyl]-N-(benzyloxy)-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 14

To a mixed liquid of 269 mg of (3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-N-enzyloxy)-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 5 ml of chloroform was added 0.21 ml of dimethylsulfamoyl chloride, followed by stirring at room temperature for 15 hours, and further at 60° C. for 24 hours. In addition, 500 mg of sodium carbonate was added thereto, followed by stirring at 60° C. for 5 hours. In addition, 0.21 ml of dimethylsulfamoyl chloride was added thereto, followed by stirring at 60° C. for 5 hours. After cooling the reaction solution, a liquid separation operation was then carried out using water and chloroform. The organic layer was washed with 1 M hydrochloric acid, a saturated aqueous sodium hydrogen carbonate solution, and a saturated aqueous sodium chloride solution, and dried over anhydrous magnesium sulfate. After evaporating the solvent, the residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain a colorless amorphous substance. The obtained amorphous substance was crystallized with ethyl acetate to obtain 99 mg of (3RS,4RS)-N-(benzyloxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(dimethylamino)sulfonylamino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 15

To a mixed liquid of 269 mg of (3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-N-enzyloxy)-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 20 ml of ethanol was added 53 mg of nitrourea, followed by heating under reflux for 1 hour. The reaction solution was cooled and then concentrated, and the residue was purified by silica gel column chromatography (eluent: chloroform-methanol), then crystallized with acetonitrile, and collected by filtration to obtain 155 mg of (3RS,4RS)-N-(benzyloxy)-2-[(1SR,2SR)-2-(carbamoylamino)cyclohexyl]-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 16

To a mixed liquid of 269 mg of (3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-N-enzyloxy)-3-(2,4-dichlorophenyl)-1-

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oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 5 ml of DMF were added 58 mg of sodium carbonate and 119 mg of methyl ethanimidothioate hydrochloride, followed by stirring at 60° C. for 1 hour. Thereafter, while stirring at 60° C., 233 mg of sodium carbonate and 478 mg of methyl ethanimidothioate hydrochloride were further added in four divided portions every 1 hour. After cooling the reaction solution, water was added thereto, followed by extraction with chloroform-isopropyl alcohol (5:1). The organic layer was dried over anhydrous magnesium sulfate and then concentrated. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol-aqueous ammonia) and then crystallized with ethyl acetate to obtain 113 mg of (3RS,4RS)-N-(benzyloxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-(ethanimidoylamino)cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 17

644 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-hydroxycyclohexyl]-N-[2-(2-methoxy-6-methylpyridin-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 1.92 g of pyridine hydrochloride were mixed, followed by warming from room temperature to 200° C. over 15 minutes. The molten mixture was left to be cooled and then subjected to a liquid separation operation using water and ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain 480 mg of a low polarity product and 146 mg of a high polarity product. The low polarity product was crystallized with ethyl acetate to obtain 277 mg of (3RS,4RS)-2-[(1SR)-cyclohex-2-en-1-yl]-3-(2,4-dichlorophenyl)-N-[2-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (Example 17-1) as a white crystal. The high polarity product was recrystallized with ethyl acetate-ethanol to obtain 85 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-hydroxycyclohexyl]-N-[2-(6-methyl-2-oxo-1,2-dihydropyridin-4-yl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide (Example 17-2) as a white crystal.

Example 18

To a mixed liquid of 456 mg of (3RS,4RS)-N-[(3-cyanobenzyl)oxy]-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 15 ml of DMF was added 139 mg of sodium azide and subsequently 114 mg of ammonium chloride at room temperature, followed by warming to 100° C. and stirring for 12 hours. The reaction solution was cooled to room temperature, then added with water, and extracted with chloroform. After drying over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by silica gel column chromatography (eluent: chloroform-methanol). The crude purified product thus obtained was recrystallized with ethanol-water to obtain 171 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-[[3-(2H-tetrazol-5-yl)benzyl]oxy]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 19

A mixture of 730 mg of tert-butyl(3-[[[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)

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amino]cyclohexyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]oxy)methyl]phenoxy]acetate, 5 ml of dichloroethane, and 5 ml of trifluoroacetic acid was stirred at room temperature for 2 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluent: chloroform-methanol). The crude purified product thus obtained was recrystallized from ethyl acetate to obtain 184 mg of (3-[[[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]oxy)methyl]phenoxy]acetic acid as a colorless crystal.

Example 20

To a solution of 330 mg of 3-[[[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]oxy)methyl]benzoic acid in 5 ml of DMF was added 122 mg of CDI, followed by stirring at room temperature for 30 minutes. To the reaction solution were added 71 mg of methane sulfonamide and 0.11 ml of DBU, followed by stirring at room temperature for 3 hours. To the reaction solution was added ethyl acetate, followed by washing with 1 M hydrochloric acid and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was then evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain a crude purified product. This was recrystallized with acetonitrile-water to obtain 273 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-N-[(3-[(methylsulfonyl)carbamoyl]benzyl]oxy)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 21

To a solution of 128 mg of (3RS,4RS)-N-(cyanomethoxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 1.92 ml of methanol was added 0.018 ml of a hydroxylamine solution at room temperature, followed by warming to 40° C. and stirring overnight. The reaction solution was cooled to room temperature and the precipitated crystal was then collected by filtration to obtain 26 mg of (3RS,4RS)-N-[2-amino-2-(hydroxyimino)ethoxy]-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 22

To a mixed liquid of 300 mg of (3RS,4RS)-N-[(3-[amino(hydroxyimino)methyl]benzyl]oxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 30 ml of acetonitrile were added 132 mg of 1,1'-carbonothioyl bis(1H-imidazole) and 0.27 ml of DBU under ice-cooling, followed by stirring at room temperature for 1 hour. The reaction solution was concentrated and then added with 50 ml of water, and 1 M hydrochloric acid was added thereto until the pH reached 4 to 5. After extracting with ethyl acetate, washing with a saturated aqueous sodium chloride solution and drying over anhydrous magnesium sulfate, the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol). The crude

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purified product thus obtained was added with ethyl acetate and collected by filtration to obtain 61 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-[[3-(5-thioxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzyl]oxy]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white solid.

Example 23

To a mixed liquid of 280 mg of (3RS,4RS)-N-[(3-[amino(hydroxyimino)methyl]benzyl]oxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 10 ml of DMF were added 0.037 ml of pyridine and subsequently 0.084 ml of 2-ethylhexyl chloroformate under ice-cooling, followed by stirring under ice-cooling for 30 minutes. To the reaction solution was added ethyl acetate, followed by washing with water and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and the solvent was then evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain 305 mg of (3RS,4RS)-N-[(3-[amino[(2-ethylhexyl)oxy]carbonyl]oxy)imino]methyl]benzyl]oxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white amorphous substance. To 290 mg of the present compound was added 6 ml of NMP, followed by stirring at 140° C. for 3 hours. The reaction solution was cooled, and 50 ml of water was then added thereto, followed by stirring. The precipitated solid was collected by filtration. This solid was purified by silica gel column chromatography (eluent: chloroform-methanol), then crystallized with acetonitrile-water, and collected by filtration to obtain 101 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-[[3-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)benzyl]oxy]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 24

To a solution of 500 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-[(1-trityl-1H-1,2,4-triazol-3-yl)methoxy]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 7.5 ml of methanol was added dropwise 0.25 ml of concentrated hydrochloric acid under ice-cooling, followed by stirring at room temperature for 4 hours. To the reaction solution was added a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with chloroform. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) and recrystallized from ethyl acetate to obtain 282 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-(1H-1,2,4-triazol-3-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 25

A solution of 400 mg of (3RS,4RS)-6-(benzyloxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 245 mg of pentamethylbenzene in 15 ml of trifluoroacetic acid was

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stirred at room temperature overnight. The trifluoroacetic acid was evaporated under reduced pressure, and ethyl acetate and water were added thereto to carry out a liquid separation operation. The organic layer was washed with a saturated aqueous sodium chloride solution, dried over anhydrous sodium sulfate, and then evaporated under reduced pressure. The residue was solidified with ethyl acetate-isopropyl alcohol and collected by filtration to obtain 350 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-6-hydroxy-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white solid.

Example 26

To a solution of 644 mg of (3RS,4RS)-N-[(4-tert-butoxybenzyl)oxy]-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 8.4 ml of dichloromethane was added 0.94 ml of trifluoroacetic acid under ice-cooling, followed by stirring at room temperature for 1 hour. The solution was concentrated under reduced pressure and then recrystallized from ethyl acetate to obtain 363 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-hydroxy-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 27

To a mixed liquid of 350 mg of ethyl 1,2-cis-2-[3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-4-[(2-phenylethyl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl]cyclohexanecarboxylate, 25 ml of THF, and 25 ml of ethanol was added 1 ml of a 1 M aqueous sodium hydroxide solution, followed by stirring at room temperature for 60 hours, and further at 60° C. for 8 hours. After evaporating the solvent, a liquid separation operation was carried out using 1 M hydrochloric acid and chloroform. The organic layer was dried over anhydrous magnesium sulfate and the solvent was then evaporated. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol). The obtained residue was washed with diisopropyl ether-ethyl acetate to obtain 144 mg of ethyl 1,2-trans-2-[3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-4-[(2-phenylethyl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl]cyclohexanecarboxylate as a white solid.

Example 28

To a mixed liquid of 334 mg of 2-(trimethylsilyl)ethyl 1,2-cis-2-[3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-4-[(pyridin-2-ylmethoxy)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl]cyclohexanecarboxylate and 5 ml of THF was added 0.60 ml of a 1 M solution of tetrabutylammonium fluoride in THF, followed by stirring at room temperature for 4 hours. To the reaction solution was added 20 ml of DMF, followed by stirring at room temperature for 2 hours, then evaporating the THF under reduced pressure, and stirring again at room temperature for 20 hours. The reaction solution was warmed to 60° C. and stirred for 2 hours, and then 0.30 ml of a 1 M solution of tetrabutylammonium fluoride in THF was further added thereto, followed by stirring at 60° C. for 2 hours. After evaporating the solvent under reduced pressure, 1 M hydrochloric acid was added, and a 1 M aqueous sodium hydroxide solution was added thereto until the pH reached 2. The solution was extracted with ethyl acetate and chloroform, and dried over anhydrous magnesium sulfate, and the solvent was then evaporated. The residue was purified by silica gel col-

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umn chromatography (eluent:chloroform-methanol), and the obtained residue was then washed with ethyl acetate to obtain 156 mg of 1,2-cis-2-[3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-4-[(pyridin-2-ylmethoxy)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl]cyclohexanecarboxylic acid as a white solid.

Example 29

To a solution of 1000 mg of (3RS,4RS)-N-[2-amino-2-(hydroxyimino)ethoxy]-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 26 ml of dichloroethane was added dropwise 0.4 ml of pyridine, and then 0.23 ml of methyl chloro(oxo)acetate was added dropwise thereto under ice-cooling, followed by stirring at 0° C. for 10 minutes, at room temperature for 20 minutes, and at 80° C. for 2 hours. The reaction solution was cooled to room temperature, washed with 0.1 M hydrochloric acid and a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol) to obtain 670 mg of methyl 3-[[[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]oxy]methyl]-1,2,4-oxadiazole-5-carboxylate as a white amorphous substance.

Example 30

To 400 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid were added 8 ml of DMF, 243 mg of O-[3-(tetrahydro-2H-pyran-2-yl)oxy]benzyl]hydroxylamine, 159 mg of HOBt, and 243 mg of WSC, followed by stirring at room temperature for 3 hours. The reaction solution was added with ethyl acetate and water to carry out a liquid separation operation, and the organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then evaporated under reduced pressure. To the residue was added methanol, and concentrated hydrochloric acid was added dropwise thereto under ice-cooling, followed by stirring under ice-cooling for 1 hour. The precipitated crystal was collected by filtration to obtain 275 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-[(3-hydroxybenzyl)oxy]-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 31

To a solution of 323 mg of 3-[[[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]oxy]methyl]-1,2,4-oxadiazol-5-yl]methyl acetate in 6.5 ml of methanol was added 66 mg of potassium carbonate, followed by stirring at room temperature for 3 hours. To the reaction solution was added ethyl acetate, followed by washing with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol) and then recrystallized from ethyl acetate to obtain 157 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-[[5-(hydroxymethyl)-1,2,4-oxadiazol-3-

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yl]methoxy}-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 32

By condensing 4-([(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino)butanoic acid and ethylamine using WSC and HOBt in accordance with Example 1, (3RS,4RS)-3-(2,4-dichlorophenyl)-N-[4-(ethylamino)-4-oxobutyl]-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide was obtained as a colorless crystal.

Example 33

By condensing 3,4-trans-2-cyclopentyl-1-oxo-4-[(2-phenylethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and benzylamine using WSC and HOBt in accordance with Example 1, 3,4-trans-3-benzylcarbamoyl-2-cyclopentyl-1-oxo-N-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide was obtained as a colorless crystal.

Example 34

By condensing cis-4-[3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-4-[(2-phenylethyl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl]cyclohexanecarboxylic acid and 1-methylpiperazine using WSC and HOBt in accordance with Example 1, 3,4-trans-3-(2,4-dichlorophenyl)-2-[cis-4-[(4-methylpiperazin-1-yl)carbonyl]cyclohexyl]-1-oxo-N-(2-phenylethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide was obtained as a colorless crystal.

Example 35

By condensing (3RS,4RS)-2-[(1SR,2SR)-2-aminocyclohexyl]-N-benzyloxy-3-(2,4-dichlorophenyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and hydroxyacetic acid using WSC and HOBt in accordance with Example 1, (3RS,4RS)-N-(benzyloxy)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-(glycolylamino)cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide was obtained as a colorless crystal.

Example 36

By treating 3,4-trans-2-cyclopentyl-3-(3-pyridinyl)-1-oxo-N-phenylethyl-1,2,3,4-tetrahydroisoquinoline-4-carboxamide with m-chloroperbenzoic acid in accordance with Example 3, 3,4-trans-2-cyclopentyl-3-(1-oxidopyridin-3-yl)-1-oxo-N-phenylethyl-1,2,3,4-tetrahydroisoquinoline-4-carboxamide was obtained as a colorless crystal.

Example 37

By treating 3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-N-phenylethyl-2-[2-(3-pyridinyl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide with m-chloroperbenzoic acid in accordance with Example 3, 3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-N-phenylethyl-2-[2-(1-oxidopyridin-3-yl)ethyl]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide was obtained as a colorless crystal.

Example 38

By treating methyl 4-{3,4-trans-2-cyclopentyl-1-oxo-4-[(2-phenylethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinolin-

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3-yl}benzoate with a 1 M aqueous sodium hydroxide solution in accordance with Example 4, 4-{3,4-trans-2-cyclopentyl-1-oxo-4-[(2-phenylethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinolin-3-yl}benzoic acid was obtained as a colorless crystal.

Example 39

By treating ethyl 4-{3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-4-[(2-phenylethyl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}propanoate with a 1 M aqueous sodium hydroxide solution in accordance with Example 4, 4-{3,4-trans-3-(2,4-dichlorophenyl)-1-oxo-4-[(2-phenylethyl)carbamoyl]-3,4-dihydroisoquinolin-2(1H)-yl}propanoic acid was obtained as a colorless crystal.

Example 40

By treating 4-([(3RS,4RS)-trans-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-trans-2-hydroxycyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino)oxy]methyl}benzoic acid with CDI and then with sodium borohydride in accordance with Example 7, (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-1,2-trans-2-hydroxycyclohexyl]-N-{[4-(hydroxymethyl)benzyl]oxy}-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide was obtained as a colorless crystal.

Example 41

To a mixed liquid of 400 mg of (3RS,4RS)-N-[2-amino-2-(hydroxyimino)ethoxy]-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide and 40 ml of acetonitrile were added 108 mg of CDI and 0.4 ml of DBU under ice-cooling, followed by stirring at room temperature overnight. After concentrating the reaction solution, a saturated aqueous ammonium chloride solution and ethyl acetate were added thereto, followed by extraction. The organic layer was washed with saturated brine and then dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent: chloroform-methanol) and recrystallized from ethyl acetate to obtain 40 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-N-[(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)methoxy]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 42

To a mixture of 300 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid and 6 ml of DMF were added {5-[(aminooxy)methyl]pyrazin-2-yl}methyl acetate dihydrochloride, 0.16 ml of triethylamine, 119 mg of HOBt, and 200 mg of WSC, followed by stirring at room temperature for 3 hours. Ethyl acetate and water were added thereto to carry out a liquid separation operation. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and saturated brine, dried over anhydrous magnesium sulfate, and then evaporated under reduced pressure. To the residue were added 4.5 ml of methanol and 2.4 ml of a 1 M aqueous sodium hydroxide solution, followed by stirring at 0° C. for 2 hours, and then 1 M hydrochloric acid was added thereto for neutralization. Chloroform was added thereto for extraction, and the organic layer

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was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluent:chloroform-methanol) and then recrystallized from ethyl acetate to obtain 73 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-[[5-(hydroxymethyl)pyrazin-2-yl]methoxy]-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless crystal.

Example 43

To a solution of 350 mg of (3RS,4RS)-N-[2-amino-2-(hydroxyimino)ethoxy]-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 9.2 ml of dichloroethane was added dropwise 0.15 ml of pyridine. To the reaction solution was added dropwise 0.095 ml of 2-chloro-2-oxoethyl acetate under ice-cooling, followed by stirring for 10 minutes at 0° C., 20 minutes at room temperature and then heating under reflux for 8 hours. The solution was cooled to room temperature, and ethyl acetate was added thereto, followed by washing with 0.1 M hydrochloric acid and a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure.

The residue was purified by silica gel column chromatography (eluent:chloroform-methanol) to obtain 323 mg of (3-[[[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(mesyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]oxy)methyl]-1,2,4-oxadiazol-5-yl)methyl acetate.

Example 44

To a solution of 600 mg of methyl 5-[[[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino]oxy)methyl]thiophene-3-carboxylate in 40 mL of THF was added 45 mg of lithium aluminum hydride at -78° C. The solution was warmed to 0° C., followed by stirring for 3 hours. Sodium sulfate decahydrate was added thereto, followed by stirring for 1 hour. After removing sodium sulfate by filtration, the organic layer was dried by adding anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol) to obtain 162 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-[[4-(hydroxymethyl)-2-thienyl]methoxy]-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white solid.

Example 45

To a solution of 500 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-6-nitro-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 10 ml of methanol-dioxane (1:1) was added 500 mg of Raney nickel, followed by stirring for 30 minutes under a hydrogen atmosphere. The catalyst was removed by filtration and the solvent was concentrated under reduced pressure to obtain 300 mg of (3RS,4RS)-6-amino-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a black solid.

Example 46

To a solution of 300 mg of (3RS,4RS)-6-amino-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]

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cyclohexyl]-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide, 213 mg of formaldehyde, and 11 mg of sulfuric acid in 5 ml of THF was added 125 mg of sodium borohydride at 0° C., followed by stirring for 2 hours. The reaction solution was poured into ice water and the organic layer was extracted with ethyl acetate. The solution was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by reverse-phase silica gel column chromatography (eluent: acetonitrile-water) to obtain 10 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-6-(dimethylamino)-2-[(1R,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-(pyridin-2-ylmethoxy)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a yellow solid.

Example 47

A solution of 343 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-(2-hydrazino-2-oxoethoxy)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 6.9 ml of THF was cooled to 0° C., and 116 mg of 1,1'-carbonyldiimidazole and 0.12 ml of triethylamine were added thereto, followed by stirring at 0° C. for 2 hours, and then stirring at room temperature overnight. 0.1 M hydrochloric acid was added thereto, followed by extraction with ethyl acetate. The solution was washed with a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was recrystallized from ethyl acetate to obtain 221 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-N-[(5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-yl)methoxy]-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white powder crystal.

Example 48

To a mixed liquid of 420 mg of benzyl(6-[2-((3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino)ethyl]pyridin-2-yl]oxy)acetate, 5 ml of DMF, and 5 ml of ethanol was added 84 mg of 5% palladium/carbon, followed by stirring at room temperature for 15 minutes under a hydrogen atmosphere. After separating the palladium/carbon by filtration, the solvent was evaporated, and the residue was purified by silica gel column chromatography (eluent:chloroform-methanol) to obtain 78 mg of (6-[2-((3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl]amino)ethyl]pyridin-2-yl]oxy)acetic acid as a white solid.

Example 49

A solution of 480 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-[[6-(hydroxymethyl)pyridin-2-yl]methoxy]-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 4.8 ml of dichloromethane was cooled to 0° C., 4.5 mg of DMAP and 0.13 ml of pyridine were added, and then 0.7 ml of acetic anhydride was added dropwise, followed by stirring at room temperature overnight. To the reaction mixture was added water, followed by extraction with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol) to obtain (6-[[acetyl][3-(2,4-dichlorophe-

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nyl)-2-{2-[(methylsulfonyl)amino]cyclohexyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino)oxy]methyl}pyridin-2-yl)methyl acetate.

Example 50

A solution of 714 mg of (3R,4R)-3-(2,4-dichlorophenyl)-N-{1-[6-(hydroxymethyl)pyridin-2-yl]ethyl}-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 14.3 ml of chloroform was cooled to 0° C., and 0.23 ml of triethylamine, 0.16 ml of acetic anhydride, and 6.8 mg of DMAP were added thereto in this order, followed by stirring at room temperature for 5 hours. The reaction solution was concentrated under reduced pressure, and ethyl acetate-water was added thereto for liquid separation, followed by washing with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution. The solution was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure to obtain {6-[1-((3R,4R)-3-(2,4-dichlorophenyl)-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino)ethyl]pyridin-2-yl}methyl acetate.

Example 51

To 591 mg of [(3R,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino)oxy]acetic acid were added 8 ml of DMF, 200 mg of tert-butyl hydrazinecarboxylate, 205 mg of HOBt, and 388 mg of WSC hydrochloride, followed by stirring at room temperature for 3 hours. Ethyl acetate and water were added thereto to carry out a liquid separation operation. The organic layer was washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, and then evaporated under reduced pressure. 7.7 ml of dichloromethane was added thereto, followed by cooling to 0° C., and 1.2 ml of trifluoroacetic acid was added thereto, followed by stirring at room temperature for 5 hours. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol) and recrystallized from ethyl acetate to obtain 417 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-(2-hydrazino-2-oxoethoxy)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white powder crystal.

Example 52

A solution of 153 mg of (6-[[[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino)oxy]methyl]-1-oxidopyridin-3-yl)methyl benzoate in 3 ml of ethanol was cooled to 0° C., and 32 mg of sodium hydroxide was added thereto, followed by stirring at 0° C. for 2 hours. The solution was neutralized with 1 M hydrochloric acid, and a saturated aqueous sodium hydrogen carbonate solution and chloroform were added for liquid separation. The organic layer was dried over anhydrous magnesium sulfate and then evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol) to obtain 24 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-{[5-(hydroxymethyl)-1-oxidopyridin-2-yl]methoxy}-2-[(1SR,2SR)-2-

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[(methylsulfonyl)amino]cyclohexyl}-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide.

Example 53

To a solution of 700 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid, 351 mg of 1-phenylmethanesulfonamide, and 334 mg of DMAP in 10.5 ml of DMF was added 525 mg of WSC/hydrochloride, followed by stirring at room temperature overnight. 0.1 M hydrochloric acid was added thereto, followed by extraction with ethyl acetate. The organic layer was washed with a saturated aqueous sodium chloride solution, then dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol), and ethyl acetate and a saturated aqueous sodium hydrogen carbonate solution were then added thereto for liquid separation. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. Ethyl acetate and diisopropyl ether were added thereto, and the precipitated solid was collected by filtration to obtain 33 mg of (3RS,4RS)-N-(benzylsulfonyl)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless solid.

Example 54

To a solution of 566 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-N-[(2,2-dimethyl-4H-[1,3]dioxin[5,4-b]pyridin-6-yl)methoxy]-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide in 11.3 ml of THF was added 3.2 ml of 1 M hydrochloric acid, followed by stirring at room temperature for 2 hours. 1.6 ml of 1 M hydrochloric acid was further added, followed by stirring for 2 days. The solution was neutralized with a saturated aqueous sodium hydrogen carbonate solution and then extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol) and recrystallized from ethyl acetate to obtain 196 mg of rel-(3RS,4RS)-3-(2,4-dichlorophenyl)-N-{[5-hydroxy-6-(hydroxymethyl)pyridin-2-yl]methoxy}-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a white crystal.

Example 55

To a solution of 433 mg of 6-[[[acetyl {3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino)oxy]methyl]-1-oxidopyridin-2-yl)methyl acetate in 8.7 ml of methanol was added 160 mg of potassium carbonate, followed by stirring. The solution was added with 1 M hydrochloric acid and then with a saturated aqueous sodium hydrogen carbonate solution, extracted with ethyl acetate, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent:chloroform-methanol). Ethyl acetate, ethanol, and diisopropyl ether were added thereto for solidification to obtain 164 mg of 3-(2,4-dichlorophenyl)-N-{[6-(hydroxymethyl)-1-oxidopyridin-2-yl]

63

methoxy}-2-[2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless solid.

Example 56

To a solution of 777 mg of {6-[1-({[(3R,4R)-3-(2,4-dichlorophenyl)-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino)ethyl]-1-oxidopyridin-2-yl)methyl acetate in 17 ml of methanol was added 0.21 ml of hydrazine monohydrate, followed by stirring for one week. Ethyl acetate was added thereto, followed by stirring for a while and concentrating, and the residue was purified by silica gel column chromatography (eluent:chloroform-methanol). Ethyl acetate and diisopropyl ether were used to make a powder, thereby obtaining 501 mg of (3R,4R)-3-(2,4-dichlorophenyl)-N-[1-[6-(hydroxymethyl)-1-oxidopyridin-2-yl]ethyl]-2-[(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless solid.

Example 57

A mixture of 590 mg of 3-[[{[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino]oxy]methyl]benzoic acid, 217 mg of CDI, and 9 ml of DMF was stirred at 50° C. for 1 hour, and 241 mg of guanidine carbonate was then added thereto, followed by stirring at the same temperature for 3 hours. The reaction solution was left to be cooled and the solvent was then evaporated under reduced pressure. The residue was diluted with ethyl acetate, and washed with a saturated aqueous sodium hydrogen carbonate solution and then with a saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent:chloroform-methanol) and recrystallized from acetonitrile to obtain 348 mg of (3RS,4RS)-N-({3-[(diaminomethyl)ene]carbonyl}benzyl)oxy-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-[(methylsulfonyl)amino]cyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide as a colorless solid.

Example 58

To a mixture of 990 mg of 4-methoxybenzyl(3-{2-[[{[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-hydroxycyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino]ethyl}phenyl)acetate and 10 ml of ethyl-ene chloride was added 10 ml of trifluoroacetic acid at room temperature, followed by stirring for 4 hours. The reaction solution was concentrated under reduced pressure. The residue was dissolved in 20 mL of methanol, and 20 mL of a saturated aqueous sodium hydrogen carbonate solution was added thereto at room temperature, followed by stirring for 30 minutes. The organic solvent was evaporated under reduced pressure, and the residue was diluted with ethyl acetate and neutralized with 1 M hydrochloric acid. The product was extracted with ethyl acetate, and the organic layer was washed with a saturated aqueous sodium chloride solution and then dried over anhydrous magnesium sulfate. The organic layer was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (eluent:chloroform-methanol) to obtain 339 mg of (3-{2-[[{[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-hy-

64

droxycyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino]ethyl}phenyl)acetic acid as a colorless solid.

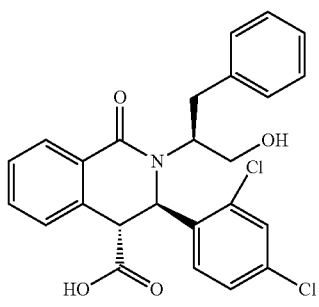
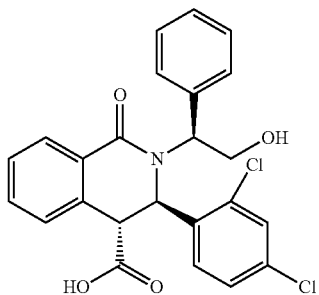
Example 59

To a mixture of 980 mg of (3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-hydroxycyclohexyl]-N-[2-(3-hydroxyphenyl)ethyl]-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide, 1160 mg of triphenylphosphine, 1080 mg of tert-butyl(2R)-2-hydroxypropanate, and 30 mL of THF was added 770 mg of diethyl azodicarboxylate at room temperature, followed by stirring for 12 hours. The reaction solution was diluted with ethyl acetate and washed with a saturated aqueous sodium hydrogen carbonate solution. The organic layer was dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (eluent: chloroform-methanol) to obtain 1460 mg of tert-butyl(2S)-2-(3-{2-[[{[(3RS,4RS)-3-(2,4-dichlorophenyl)-2-[(1SR,2SR)-2-hydroxycyclohexyl]-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino]ethyl}phenoxy)propanate as a yellow solid.

The compounds of Examples 60 to 899 as shown in Tables below were prepared in the same manner as the methods of Examples 1 to 59, using each of the corresponding starting materials. The structures of each Example Compound are shown in Tables 70 to 275, and the production processes and the physicochemical data of each Example Compound are shown in Tables 276 to 300.

Furthermore, the structures of the other compounds of the present invention are shown in Tables 301 to 302. These can be easily synthesized by using the production processes as described above, the methods described in Examples, methods obvious to a skilled person in the art, or modified methods thereof.

TABLE 14

PEx	Syn	Structure	Data	Note
64	P34		ESI+: 471	
65	P34		ESI+: 456	

65

TABLE 14-continued

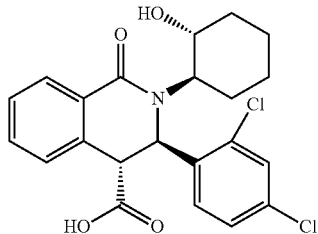
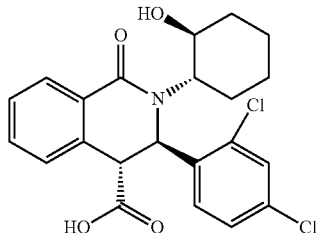
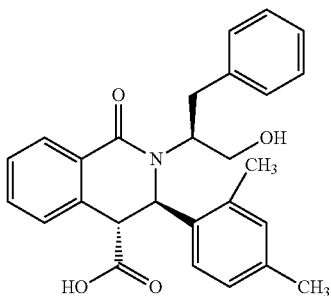
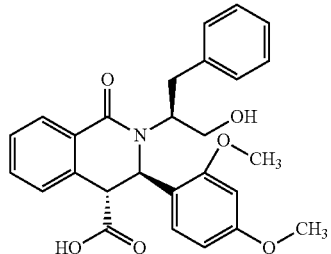
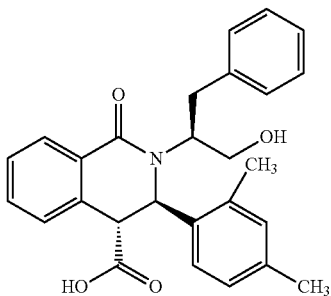
PEx	Syn	Structure	Data	Note
34-2	P34		ESI+: 434	racemic mixture
34-1	P34		ESI-: 434	racemic mixture
66	P34		ESI+: 430	

TABLE 15

67	P34		ESI+: 462	
68	P34		ESI+: 430	

66

TABLE 15-continued

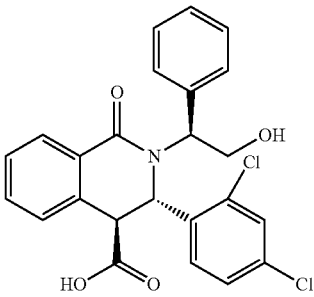
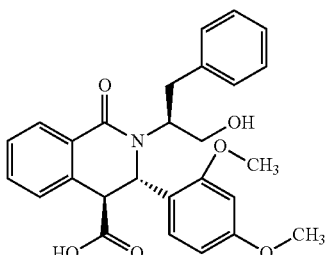
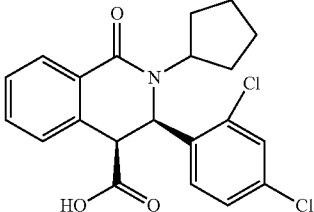
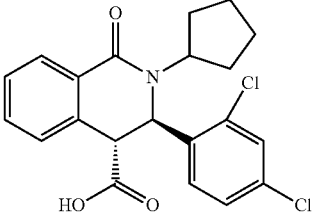
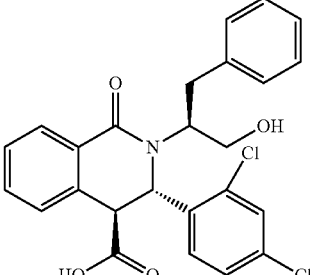
69	P34		ESI+: 456	
70	P34		ESI+: 462	
33-1	P33		ESI+: 404	racemic mixture

TABLE 16

33-2	P33		ESI+: 404	racemic mixture	
55	71	P34		ESI+: 471	

67

TABLE 16-continued

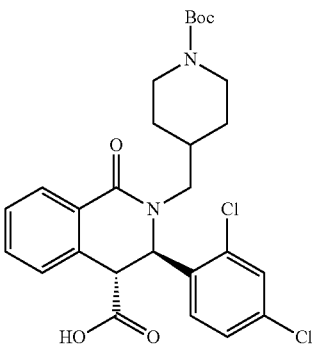
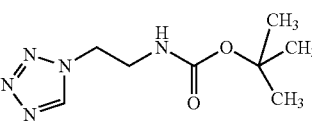
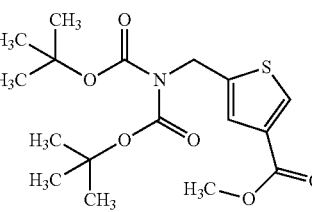
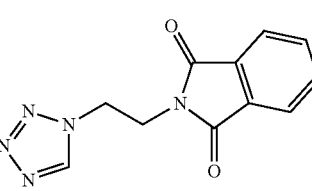
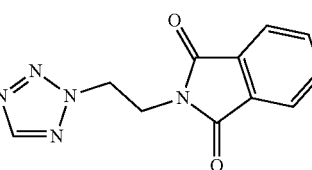
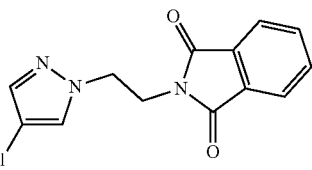
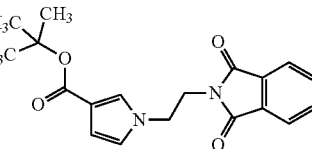
72	P33		FAB+: 532	racemic mixture
30	P30		ESI+: 214	
18	P18		FAB+: 372	
73	P31		ESI+: 244	
74	P31		ESI+: 244	

TABLE 17

75	P31		ESI+: 276	
31	P31		FAB+: 340	

68

TABLE 17-continued

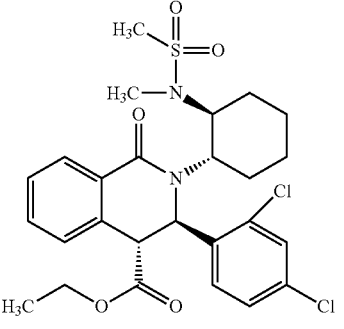
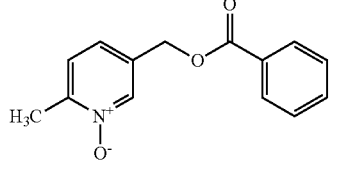
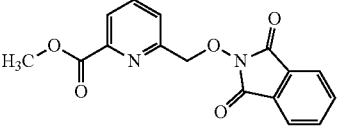
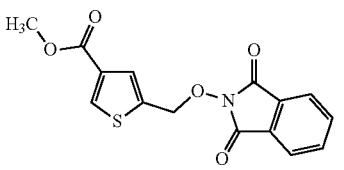
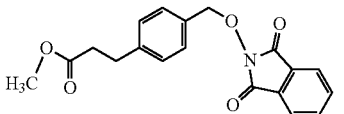
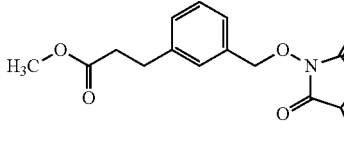
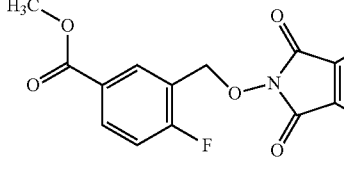
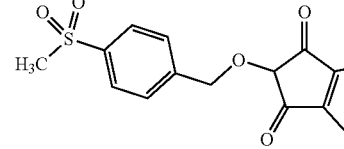
37	P37		ESI+: 553	racemic mixture
5	P5		FAB+: 244	
76	P17		FAB+: 313	
77	P14		FAB+: 318	
78	P42		FAB+: 340	

TABLE 18

79	P42		FAB+: 340	
80	P14		ESI+: 330	
60	14		FAB+: 332	

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TABLE 18-continued

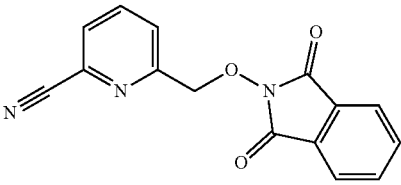
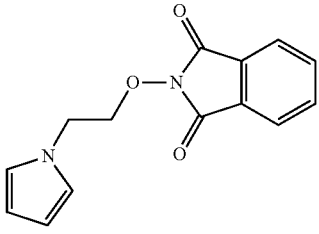
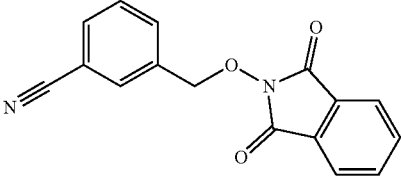
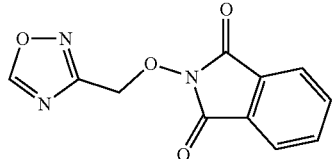
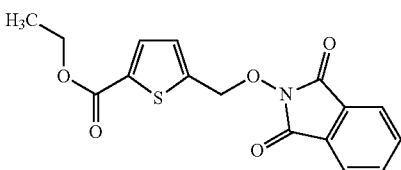
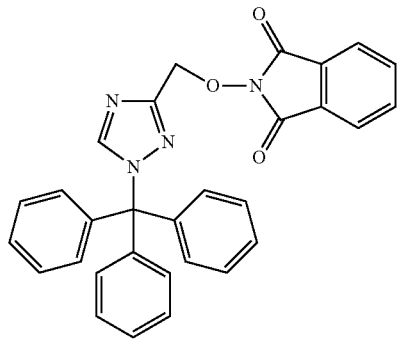
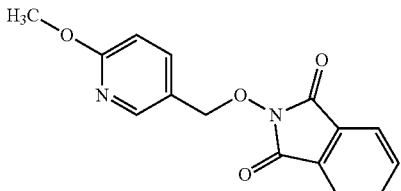
81	P14		FAB+: 280
82	P14		FAB+: 257
83	P14		FAB+: 279
84	P14		FAB+: 246
85	P14		FAB+: 332

TABLE 19

86	P14		FAB+: 487
87	P14		FAB+: 285

70

TABLE 19-continued

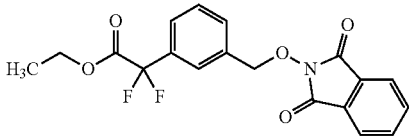
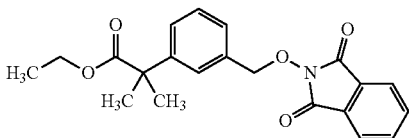
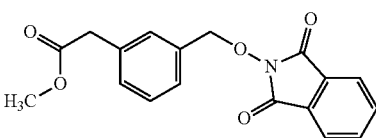
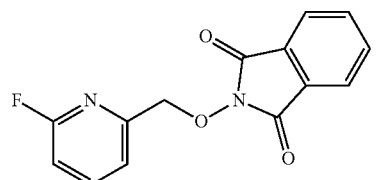
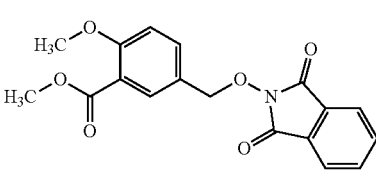
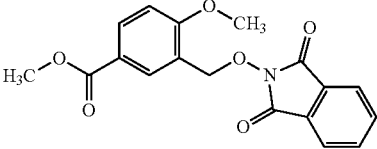
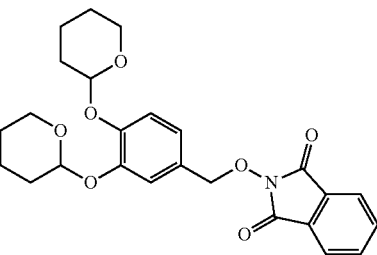
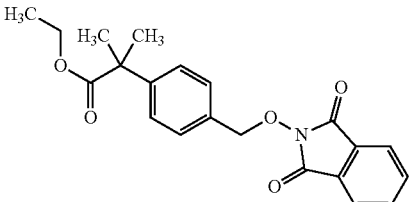
88	P14		FAB+: 376	
5				
10	89	P42		FAB+: 368
15				
90	P14		FAB+: 326	
20				
91	P14		FAB+: 273	
25				
92	P14		ESI+: 342	
30				
35				

TABLE 20

93	P14		ESI+: 342
45			
94	P42		FAB+: 454
50			
55			
95	P14		FAB+: 368
60			
65			

71

TABLE 20-continued

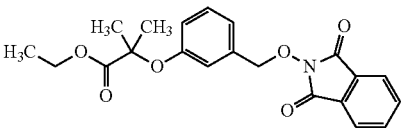
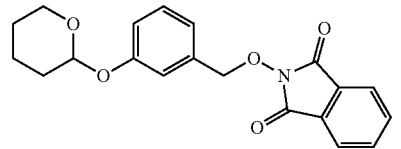
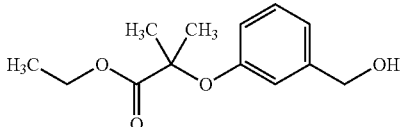
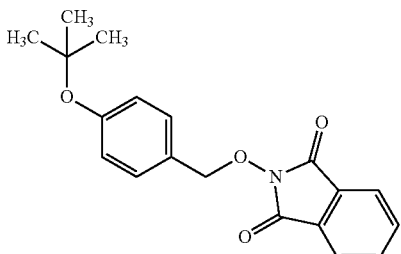
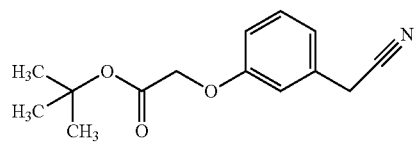
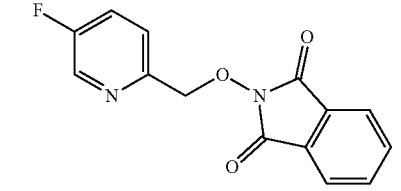
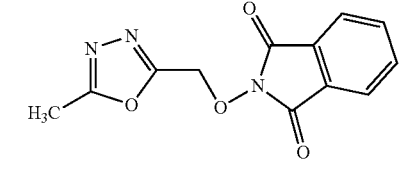
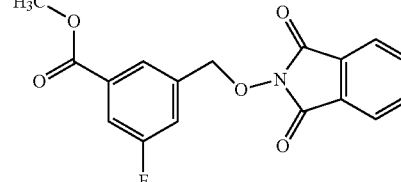
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97	P42		FAB+: 354
98	P14		EI+: 238
99	P42		FAB+: 326

TABLE 21

100	P14		EI+: 247
42	P42		FAB+: 273
101	P14		FAB+: 260
102	P14		ESI+: 330

72

TABLE 21-continued

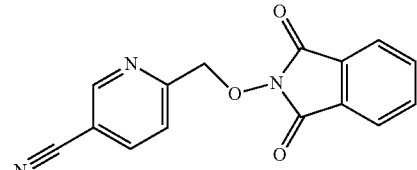
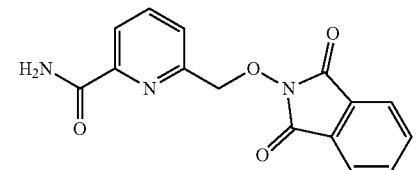
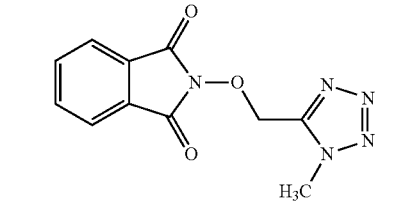
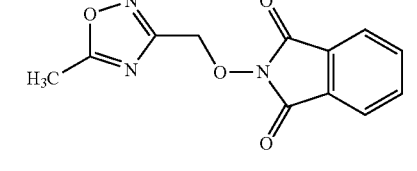
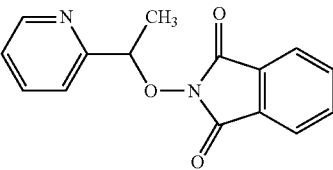
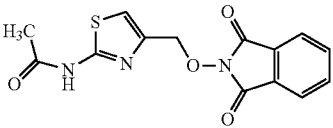
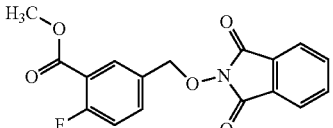
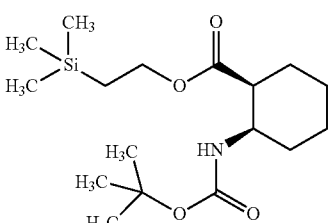
103	P14		ESI+: 280
5			
10			
104	P14		FAB+: 298
15			
105	P14		FAB+: 260
20			
25			
106	P14		FAB+: 260
30			
35			

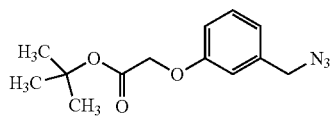
TABLE 22

107	P14		FAB+: 269	
40				
45				
108	P14		ESI+: 318	
50				
109	P14		ESI+: 330	
55				
25	P25		FAB+: 344	racemic mixture
60				
65				

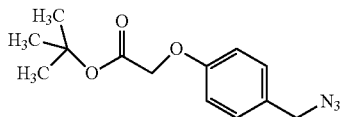
73

TABLE 22-continued

15 P15

FAB+:
263

43 P43

FAB+:
263

110 11

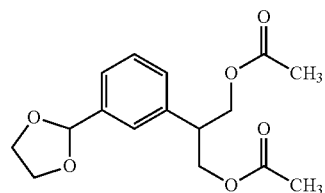
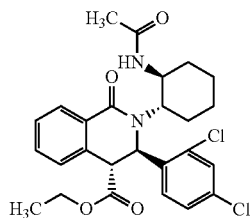
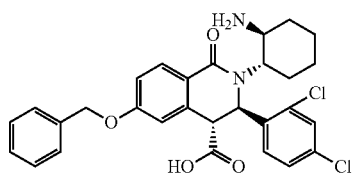
ESI+:
309

TABLE 23

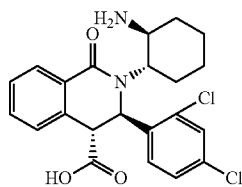
111 11

FAB+:
503
racemic mixture

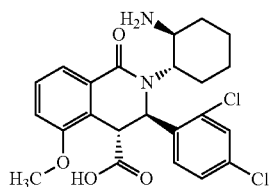
112 P34

FAB+:
539
racemic mixture

113 P34

ESI+:
433

114 P34

FAB+:
463
racemic mixture

115 P34

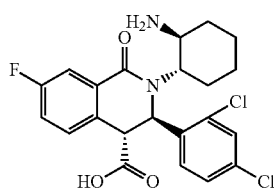
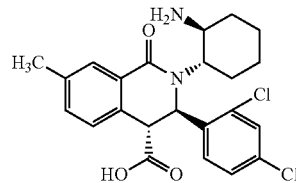
FAB+:
451
racemic mixture**74**

TABLE 23-continued

116 P34

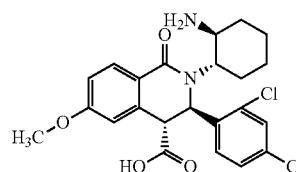
FAB+:
447
racemic mixture

5

10

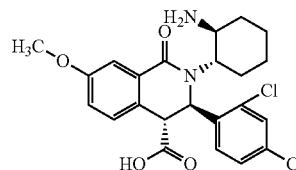
TABLE 24

15 117 P34

ESI+: 463
racemic mixture

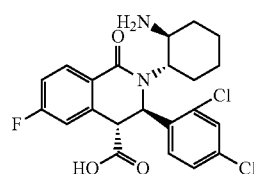
20

25 118 P34

ESI+: 463
racemic mixture

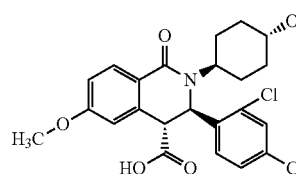
30

119 P34

FAB+: 451
racemic mixture

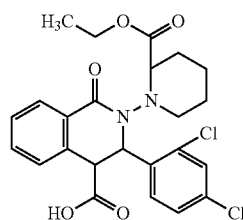
35

40 120 P34

ESI+: 465
racemic mixture

45

121 P33

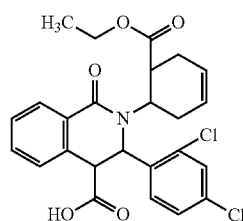


FAB+: 491

50

55

122 P33

FAB+: 488
1',2'-trans

65

75

TABLE 25

123 P33		FAB+: 562 1',2'-trans
124 P33		FAB+: 462 1',2'-trans
125 P33		FAB+: 405
126 P35		ESI+: 491 racemic mixture
127 P34 P35		ESI+: 445 1',2'-trans, 3,4-trans, diastereo mixture
35 P35		ESI+: 461 racemic mixture

TABLE 26

128 P35		ESI+: 461
11 P11		CI+: 210

76

TABLE 26-continued

17 P17		EI+: 190
20 P20		CI+: 365
19 P19		EI+: 292
4 P4		CI+: 228
21 P21		CI+: 221
129 P36		FAB+: 569 racemic mixture

TABLE 27

130 P36		FAB+: 557 racemic mixture
131 P36		FAB+: 557 racemic mixture

77

TABLE 27-continued

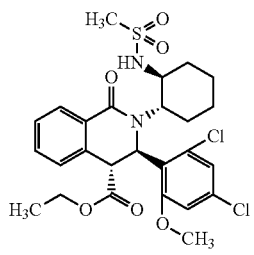
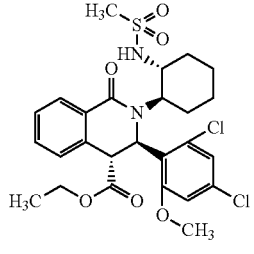
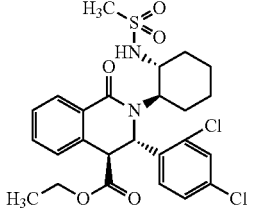
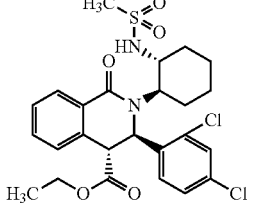
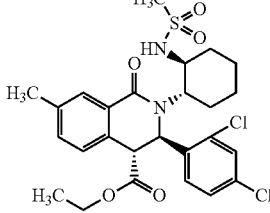
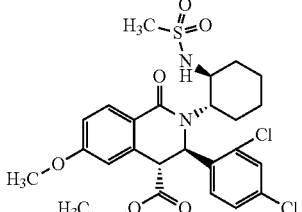
132	P34 P35 P36		FAB+: 569	racemic mixture
133	P34 P35 P36		FAB+: 569	racemic mixture

TABLE 28

134	P34 P35 P36		FAB+: 539	racemic mixture
135	P34 P35 P36		FAB+: 539	racemic mixture
136	P36		ESI+: 553	racemic mixture
137	P36		FAB+: 569	racemic mixture

78

TABLE 28-continued

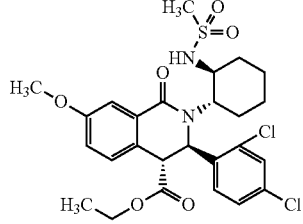
138	P36		ESI+: 569	racemic mixture
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TABLE 29

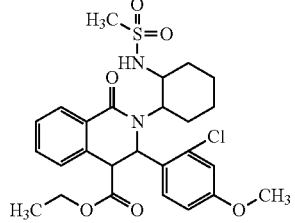
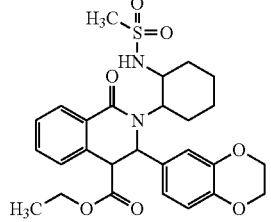
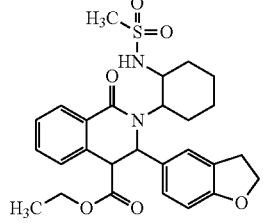
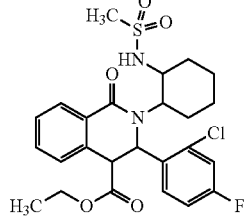
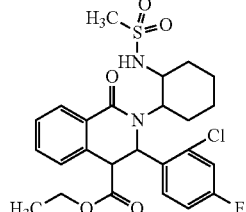
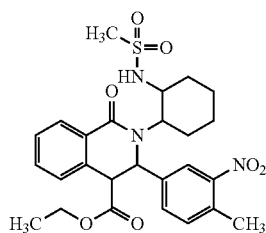
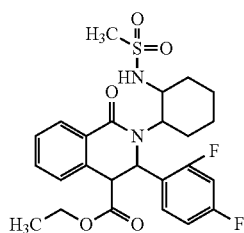
139	P34 P35 P36		ESI+: 535	1',2'-trans, 3,4-trans, racemic mixture
140	P34 P35 P36		FAB+: 529	1',2'-trans, 3,4-trans, racemic mixture
141	P34 P35 P36		FAB+: 513	1',2'-trans, 3,4-trans, racemic mixture
142	P36		ESI+: 523	1',2'-trans, 3,4-trans, racemic mixture

TABLE 30

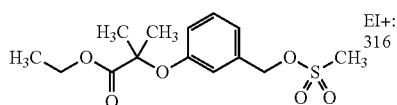
143	P36		ESI+: 523	1',2'-trans, 3,4-trans, racemic mixture
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79

TABLE 30-continued

144 P35
P36ESI+: 530
1',2'-trans,
3,4-
trans,
race-
mic
mix-
ture145 P34
P35
P36FAB+: 507
1',2'-
trans,
3,4-
trans,
race-
mic
mix-
ture

146 P36



EI+: 316

147 P36

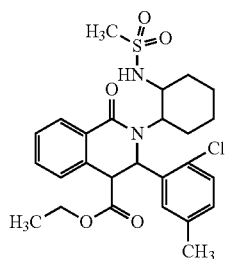
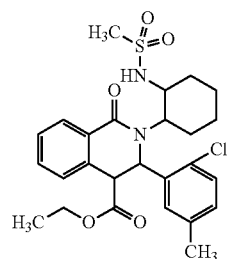
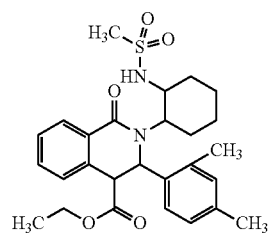
ESI+: 519
1',2'-
trans,
3,4-
trans,
race-
mic
mix-
ture,
less
polar

TABLE 31

148 P36

ESI+: 519
1',2'-trans,
3,4-trans,
racemic
mixture,
more polar

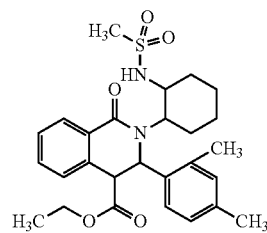
149 P36

ESI+: 499
1',2'-trans,
3,4-trans,
racemic
mixture,
less polar

80

TABLE 31-continued

150 P36

ESI+: 499
1',2'-trans,
3,4-trans,
racemic
mixture,
more polar

36 P36

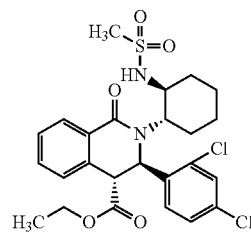
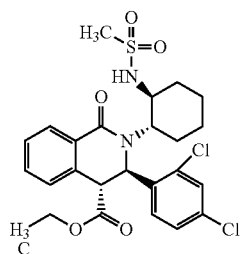
ESI+: 539
racemic
mixture

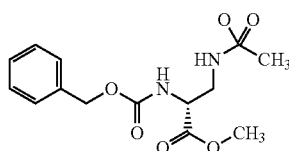
TABLE 32

151 P36



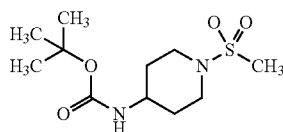
ESI+: 539

152 P22



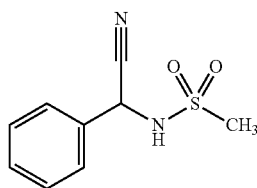
FAB+: 331

22 P22



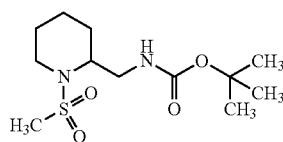
FAB+: 279

153 P22



FAB-: 209

154 P22

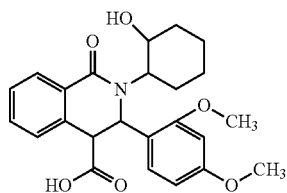


FAB+: 293

81

TABLE 32-continued

155 P34

FAB+: 426 1',2'-trans,
3,4-trans,
racemic
mixture,
less polar

82

TABLE 34

162 P34

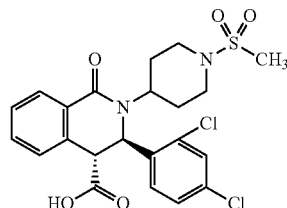
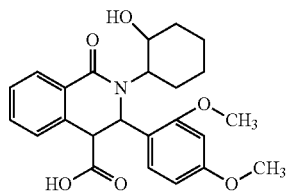
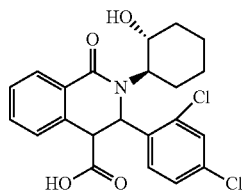
FAB+: 497 racemic
mixture

TABLE 33

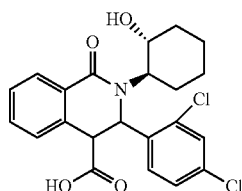
156 P34

FAB+: 426 1',2'-trans,
3,4-trans,
racemic
mixture,
more polar

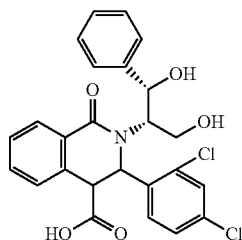
157 P34

FAB+: 434 1',2'-trans,
3,4-trans,
racemic
mixture,
less polar

158 P34

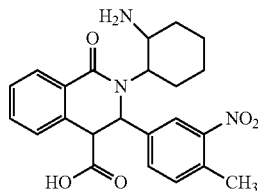
FAB+: 434 1',2'-trans,
3,4-trans,
racemic
mixture,
more polar

159 P34

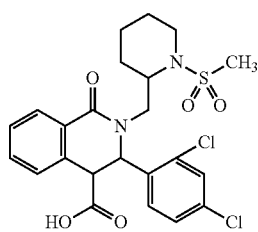


FAB+: 486

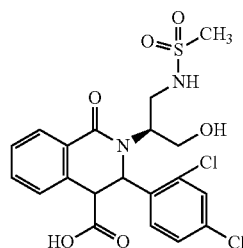
160 P34

ESI+: 424 1',2'-trans,
3,4-trans,

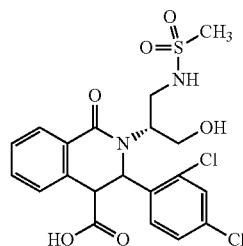
161 P34

ESI+: 511 3,4-trans,
diastereo
mixture

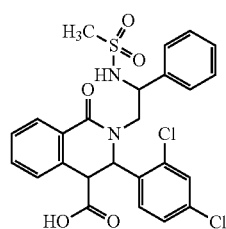
163 P34

ESI-: 485 3,4-trans,
diastereo
mixture

164 P34

ESI-: 485 3,4-trans,
diastereo
mixture

165 P34

FAB+: 533 3,4-trans,
diastereo
mixture

166 P34

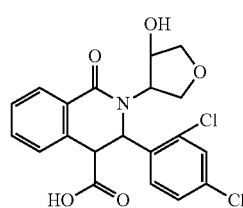
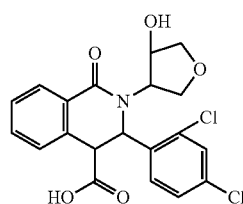
ESI+: 422 1',2'-trans,
3,4-trans,
racemic
mixture,
more polar

TABLE 35

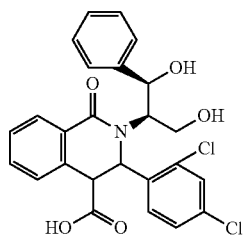
167 P34

ESI+: 422 1',2'-
trans,
3,4-
trans,
race-
mic
mix-
ture,
less
polar

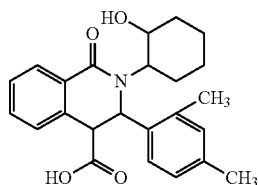
83

TABLE 35-continued

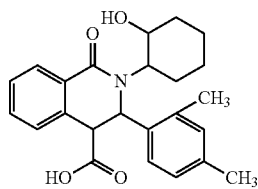
168 P34

FAB+:
486

169 P34

FAB+: 1',2'-
394 trans,
3,4-
trans,
race-
mic
mix-
ture,
less
polar

170 P34

FAB+: 1',2'-
394 trans,
3,4-
trans,
race-
mic
mix-
ture,
more
polar

171 P34

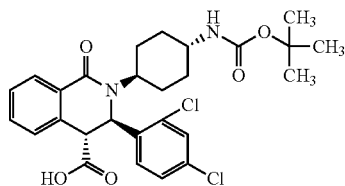
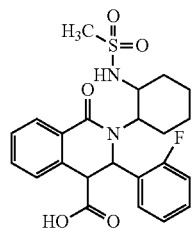
FAB-: race-
531 mic
mix-
ture

TABLE 36

172 P34
P35
P36
P38ESI+: 461 1',2'-trans,
3,4-trans,
racemic
mixture

38 P38

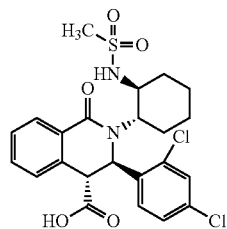
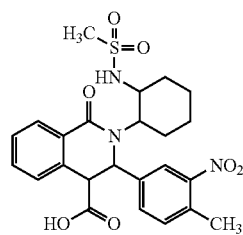
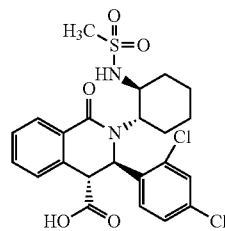
ESI+: 512 racemic
mixture**84**

TABLE 36-continued

173 P38

ESI+: 502 1',2'-trans,
3,4-trans,
racemic
mixture

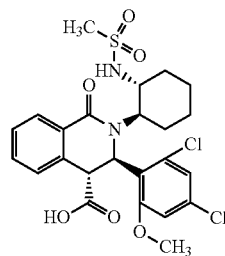
174 P38



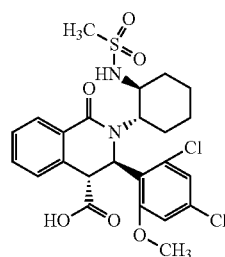
ESI+: 511

TABLE 37

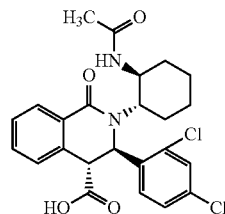
175 P38

FAB+: 541 racemic
mixture

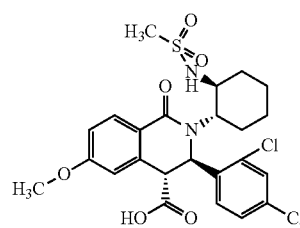
176 P38

FAB+: 541 racemic
mixture

177 P38

ESI+: 475 racemic
mixture

178 P38

FAB+: 541 racemic
mixture

85

TABLE 38

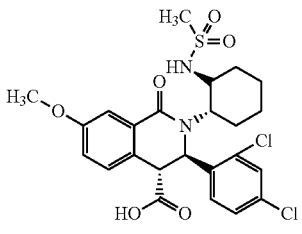
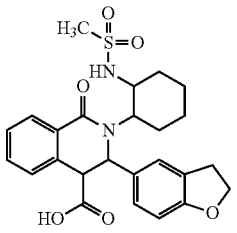
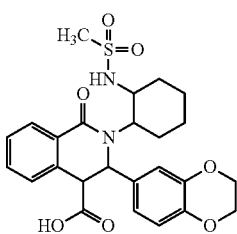
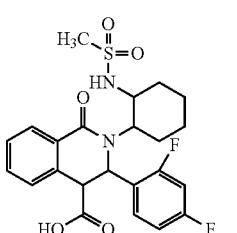
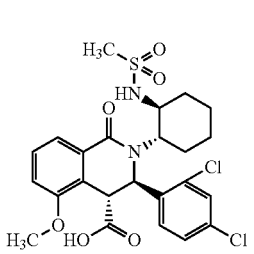
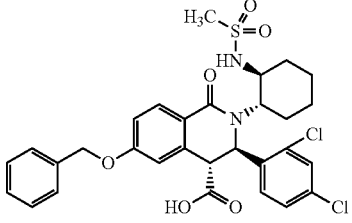
179 P38		ESI+: 541	racemic mixture
180 P38		ESI+: 485	1',2'-trans, 3,4-trans, racemic mixture
181 P38		ESI+: 501	1',2'-trans, 3,4-trans, racemic mixture
182 P38		ESI+: 479	1',2'-trans, 3,4-trans, racemic mixture
183 P38		FAB+: 541	racemic mixture

TABLE 39

184 P34 P35 P36 P38		ESI-: 617	racemic mixture
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86

TABLE 39-continued

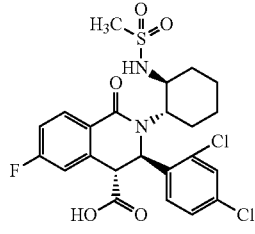
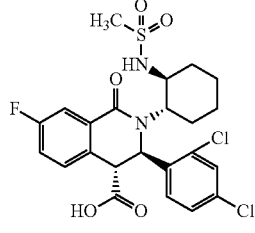
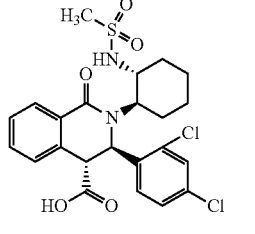
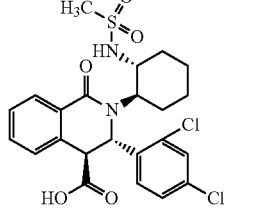
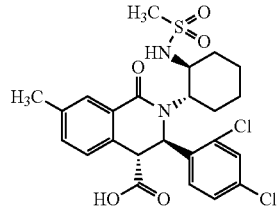
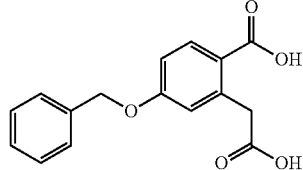
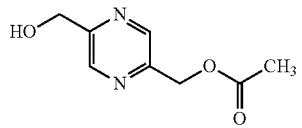
185 P38		FAB+: 529	racemic mixture
186 P38		FAB+: 529	racemic mixture
187 P38		FAB+: 511	
188 P38		FAB+: 511	

TABLE 40

189 P38		FAB+: 525	racemic mixture
1 P1		ESI-: 285	
7 P7		CI+: 183	

87

TABLE 40-continued

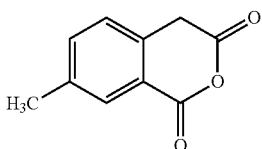
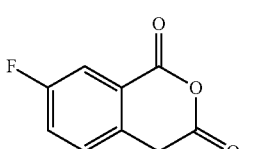
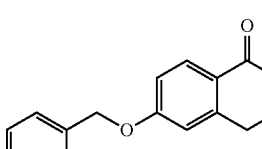
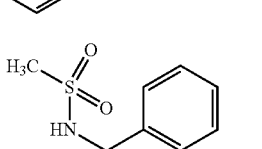
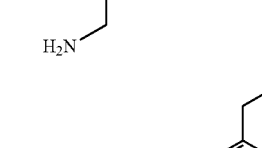
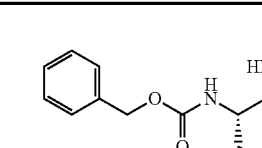
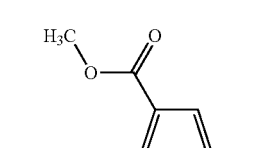
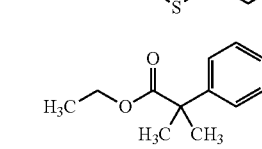
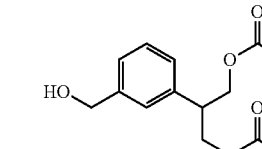
190 P39		ESI+: 177
191 P39		EI+: 180
39 P39		FAB+: 269
192 P23		FAB+: 215
23 P23		EI+: 251

TABLE 41

27 P27		FAB+: 303
16 P16		EI+: 172
193 P16		EI+: 222
194 P16		FAB+: 267

88

TABLE 41-continued

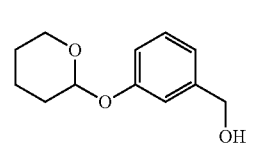
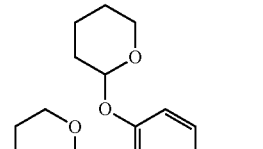
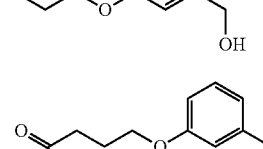
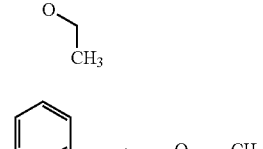
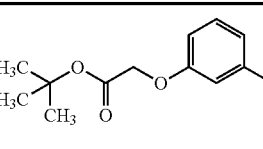
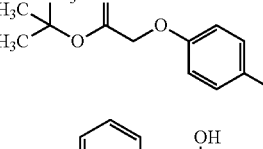
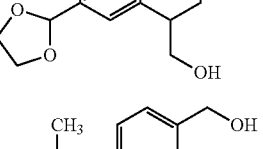
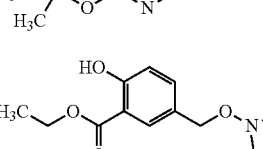
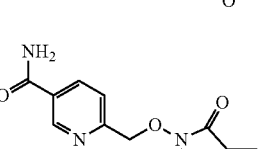
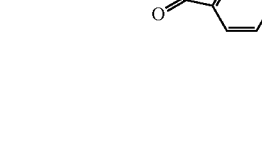
195 P16		FAB+: 209
5		
196 P16		FAB-: 307
10		
15		
197 P16		ESI: 261 [M + Na]
20		
25		
198 P16		ESI+: 239
30		

TABLE 42

24 P24		EI+: 237
35		
199 P24		EI+: 237
40		
2 P2		ESI+: 225
45		
12 P12		EI+: 181
50		
200 P8		FAB+: 342
55		
8 P8		FAB+: 298
60		
65		

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TABLE 42-continued

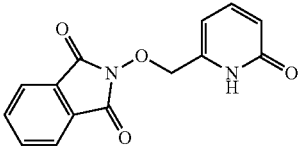
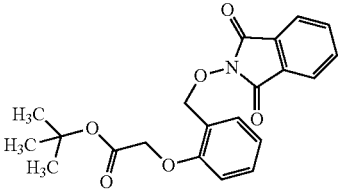
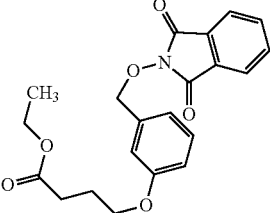
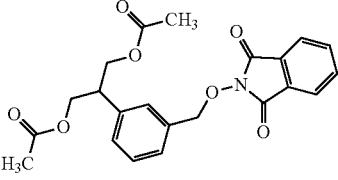
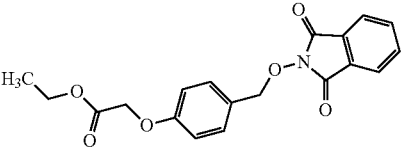
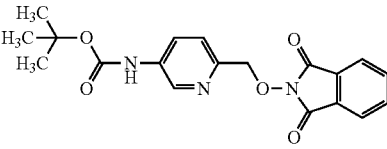
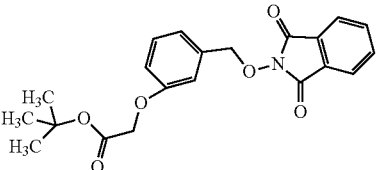
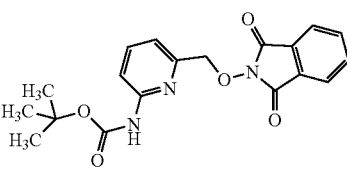
201 P8		FAB+: 271
202 P8		APCI+: 384

TABLE 43

203 P8		ESI+: 384
204 P8		ESI+: 412
205 P8		FAB+: 356
206 P8		ESI-: 368
207 P56 P8		FAB+: 383
208 P8		ESI+: 370

90

TABLE 43-continued

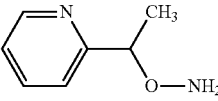
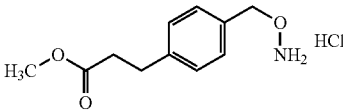
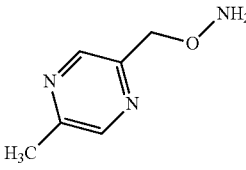
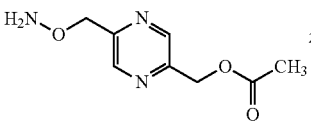
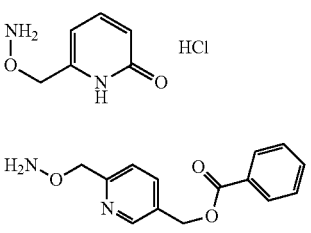
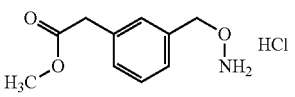
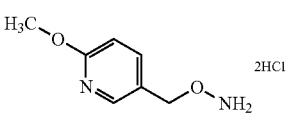
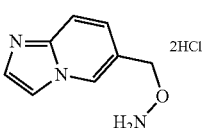
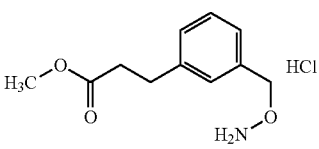
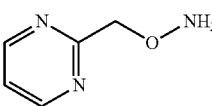
209 P8		CI+: 139
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TABLE 44

210 P40		FAB+: 210
211 P8 P40		CI+: 140
212 P8 P40		FAB+: 198
213 P8 P40		FAB+: 259
214 P40		FAB+: 196
215 P40		FAB+: 155
216 P8 P40		FAB+: 164
217 P40		FAB+: 210
218 P8 P40		FAB+: 126

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TABLE 45

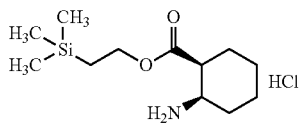
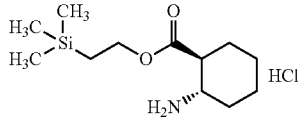
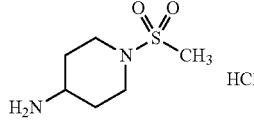
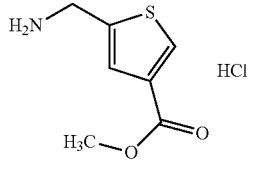
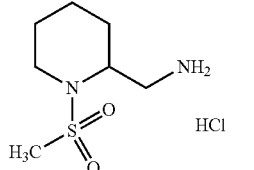
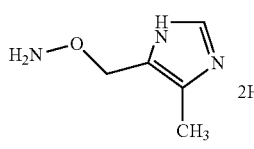
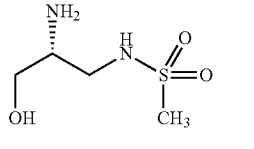
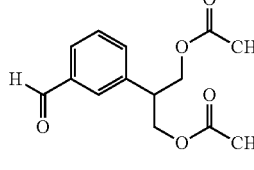
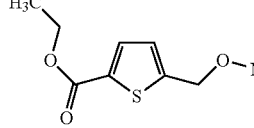
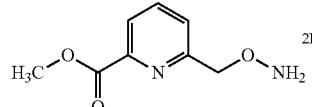
26	P26		FAB+: 244 racemic mixture
219	P25 P26		FAB+: 244 racemic mixture
220	P26		ESI+: 179
221	P26		FAB+: 172
222	P26		FAB+: 193
41	P41		FAB+: 128 2HCl
28	P28		FAB+: 169
3	P3		CI+: 265
223	P40		FAB+: 202 HCl

TABLE 46

224	P40		FAB+: 183 2HCl
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TABLE 46-continued

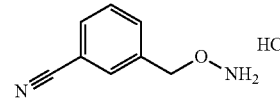
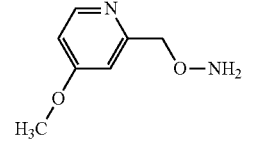
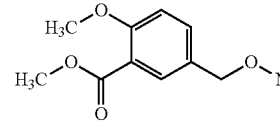
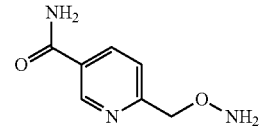
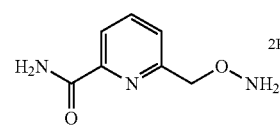
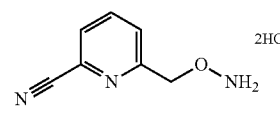
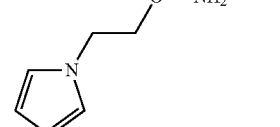
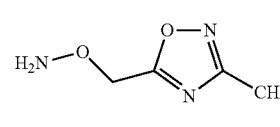
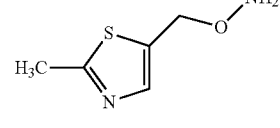
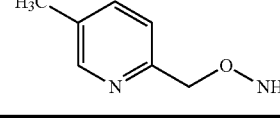
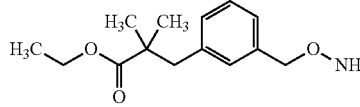
225	P40		EI+: 148
226	P14 P9		FAB+: 155
227	P9		CI+: 212
9	P9		CI+: 168
228	P40		ESI+: 168 2HCl
229	P40		FAB+: 150 2HCl
230	P9		EI+: 126
231	28 P9		CI+: 130
232	P8 P9		CI+: 145
233	P8 P9		EI+: 138

TABLE 47

234	P9		EI+: 253
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TABLE 47-continued

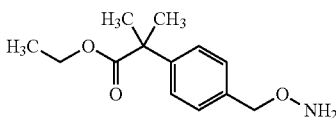
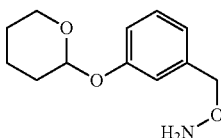
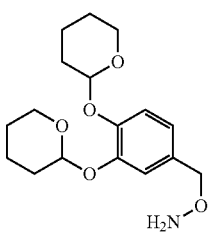
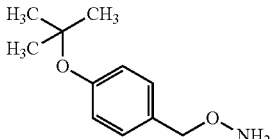
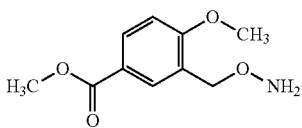
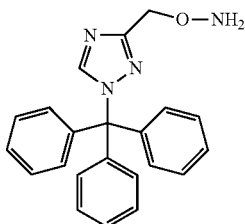
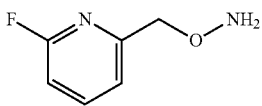
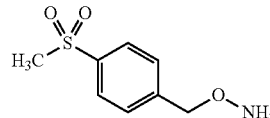
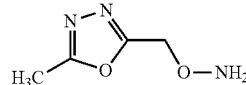
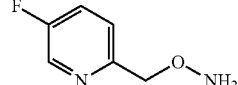
235	P9		CI+: 238
236	P9		EI+: 223
237	P9		FAB+: 324
238	P9		CI+: 196
239	P9		CI+: 212
240	P9		FAB+: 357
241	P9		CI+: 143

TABLE 48

242	P9		FAB+: 202
243	P9		CI+: 130
244	P9		CI+: 143

94

TABLE 48-continued

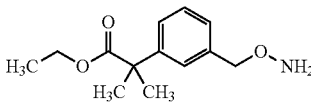
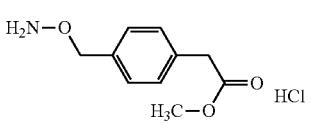
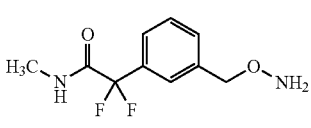
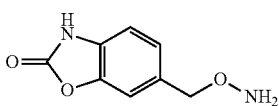
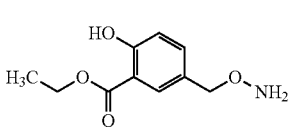
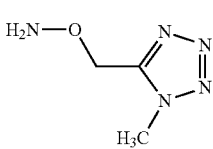
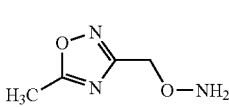
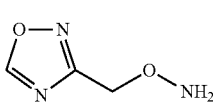
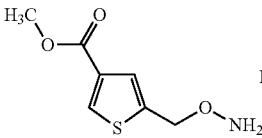
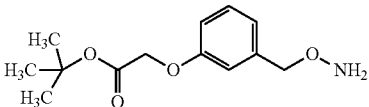
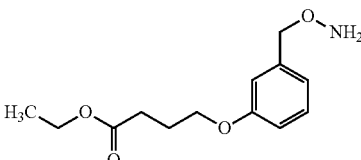
245	P9		FAB+: 238
5			
246	P14 P40		FAB+: 196
10			
247	P9		CI+: 231
15			
248	P8 P9		CI+: 180
20			
249	P9		CI+: 212
25			
250	P9		CI+: 130
30			
251	P9		CI+: 130
35			
252	P9		EI+: 115
40			
45			

TABLE 49

253	P40		FAB+: 188
50			
254	P9		ESI+: 254
55			
255	P9		ESI+: 254
60			
65			

95

TABLE 49-continued

256	P9		ESI+: 282
257	P9		CI+: 226
258	P9		ESI+: 254
259	P9		ESI+: 240
260	P9		ESI+: 200

TABLE 50

261	P9		ESI+: 200
262	P9		ESI+: 200
263	P9		ESI+: 150
264	P9		ESI+: 240

96

TABLE 50-continued

265	P32		EI+: 152
266	P32		ESI+: 114
267	P32		ESI+: 146
32	P32		ESI+: 211
13	P13		FAB+: 141 HCl
29	P29		FAB+: 139 HBr

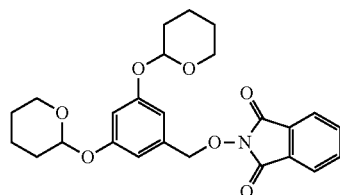
TABLE 51

10	P10		FAB+: 196
6	P6		ESI-: 242
268	P33		ESI+: 478 racemic mixture
269	P35 P36		ESI+: 584 racemic mixture

97

TABLE 51-continued

270 P42

FAB+:
454

271 P38

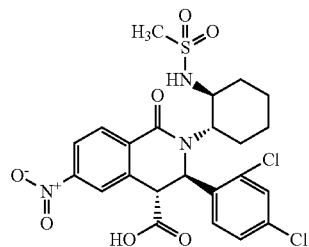
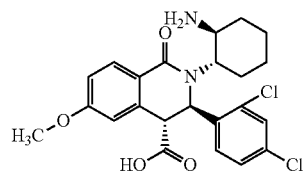
ESI+:
556
race-
mic
mix-
ture

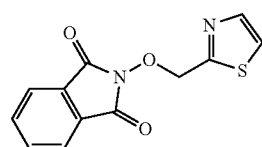
TABLE 52

272 P33



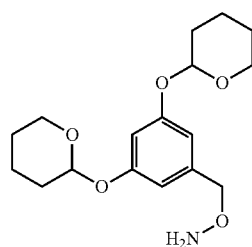
ESI+: 464

273 P42

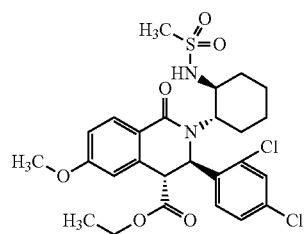


FAB+: 261

274 P9



FAB+: 324

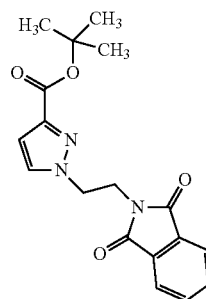
275 P35
P36

ESI+: 569

98

TABLE 52-continued

55 P55



ESI+: 342

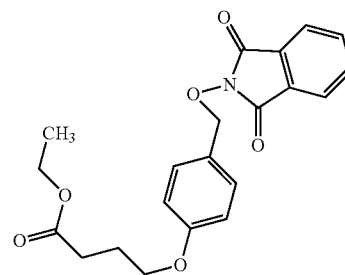
5

10

15

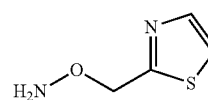
TABLE 53

276 P8

ESI+:
342

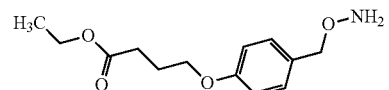
25

30

277 P9
P40FAB+:
131

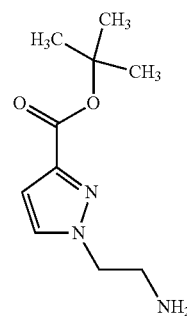
35

278 P9

ESI+:
254

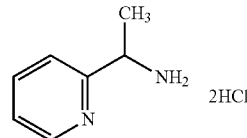
40

279 P32

ESI+:
212

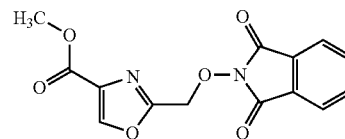
45

50

280 P51
P40ESI+:
123
2HCl

55

281 P14

ESI+:
303

60

65

99

TABLE 53-continued

282 P8		ESI+: 333
TABLE 54		
57 P57		FAB+: 240
283 P9		ESI+: 173
284 P38		EI+: 186
52 P52		EI+: 165
285 P60		CI+: 243
286 P9		FAB+: 203
62 P62		ESI+: 369
287 P32		ESI+: 212

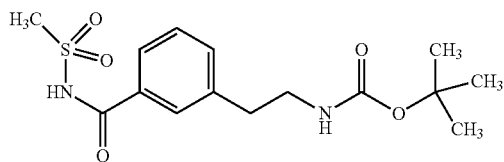
100

TABLE 55

288 20		ESI-: 327
289 P8 P9		FAB+: 203
290 P8 P9		FAB+: 181
291 P19		CI+: 321
292 P8		ESI+: 310
293 P26		FAB+: 229
294 P14		ESI+: 402
295 P9		CI+: 274
296 P9		FAB+: 180

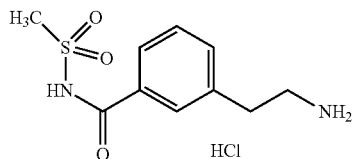
TABLE 56

297 20



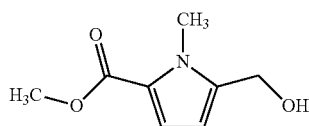
FAB-: 341

298 P26

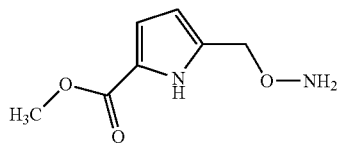


FAB+: 243

299 P16

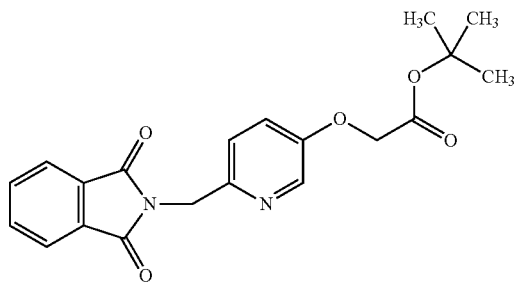


ESI+: 170

P8
300 P9

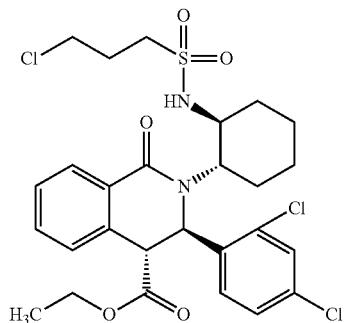
NMR1:
2.50 (2H, s),
4.50 (3H, s),
6.00 (2H, s),
6.13-6.16
(1H, m),
6.71-6.73
(1H, m),
11.84 (1H, s)

301 P62



ESI+: 269

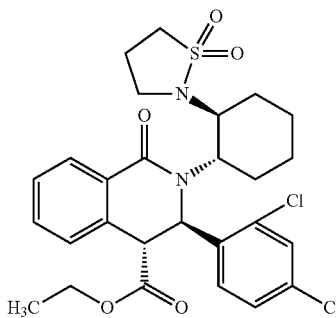
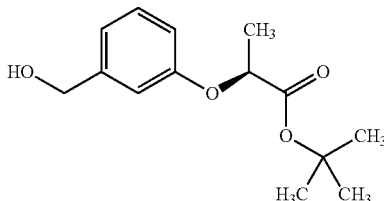
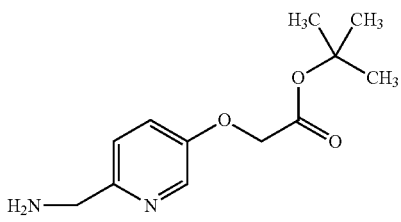
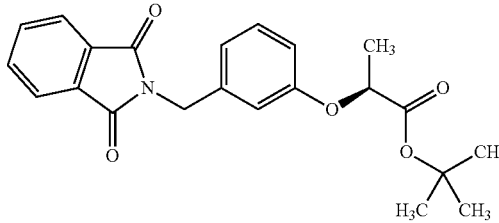
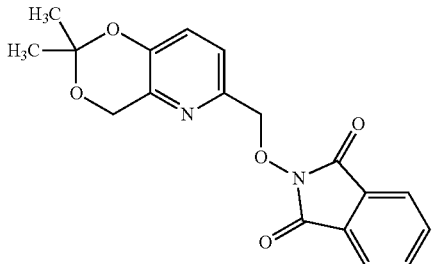
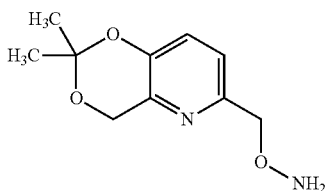
302 12



ESI+: 603

racemic
mixture

TABLE 57

44 P44		ESI+: 565 racemic mixture
58 P58		EI+: 252
303 P32		ESI+: 239
304 P62		FAB+: 381
305 P8		FAB+: 341
306 P9		CI+: 211

105

TABLE 58

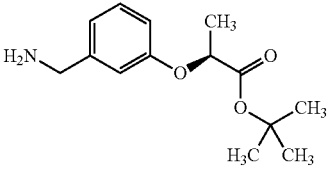
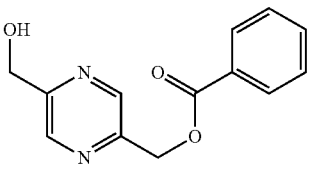
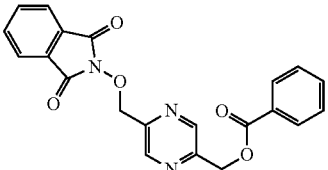
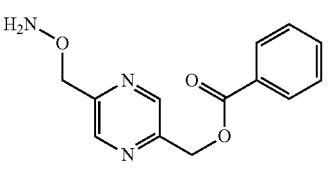
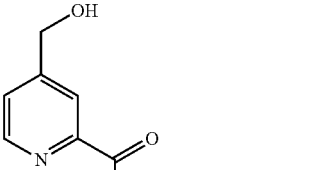
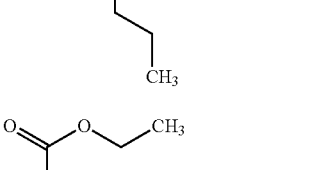
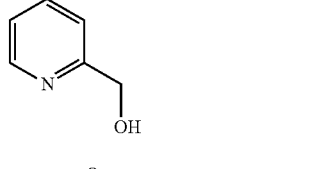
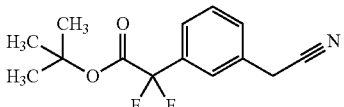
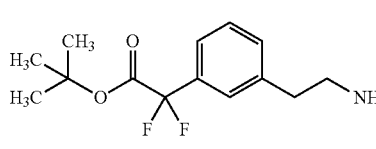
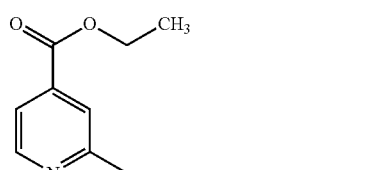
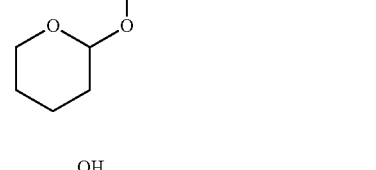
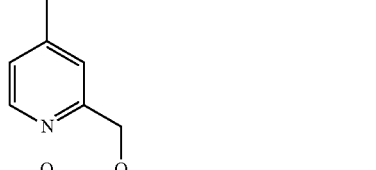
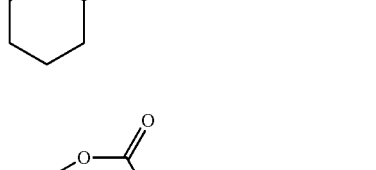
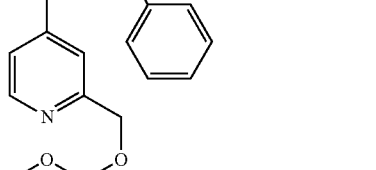
307	P32		ESI+: 252
308	P4		FAB+: 245
309	P8		FAB+: 390
310	P9		FAB+: 260
53-1	P53		CI+: 182
53-2	P53		EI+: 180
311	P14		ESI+: 316

TABLE 59

312	P48		CI+: 268
-----	-----	---	----------

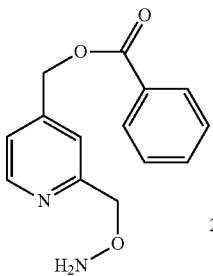
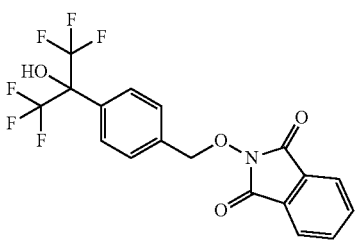
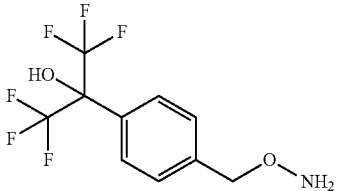
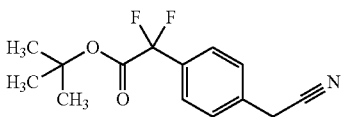
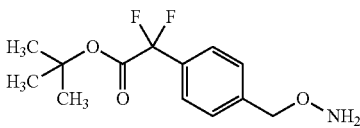
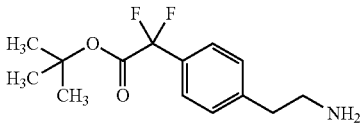
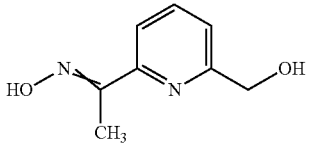
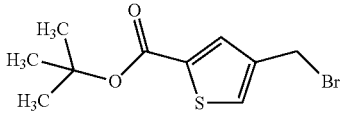
106

TABLE 59-continued

313	P23		FAB+: 272
5			
10	50 P50		FAB+: 266
15			
20			
25	314 P12		FAB+: 244
30			
35	315 P4		FAB+: 328
40			
45			
50	63 P63		FAB+: 244
55			
60	316 P14		ESI+: 332
65			

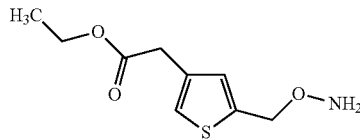
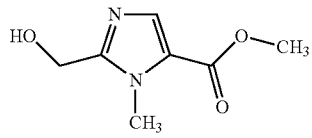
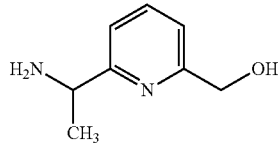
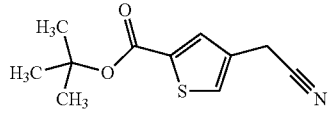
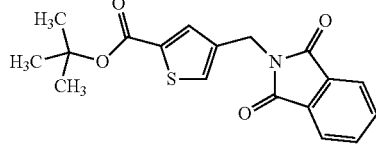
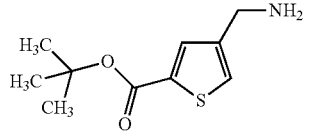
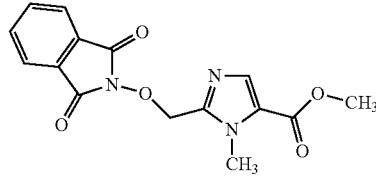
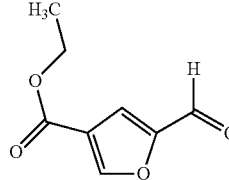
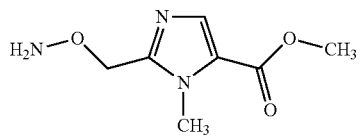
107

TABLE 60

317 P8 P9 P40		ESI+: 259
318 P14		FAB+: 420
319 P9		CI+: 290
320 P48		FAB+: 268
321 P14 P9		CI+: 274
322 P23		EI+: 271
61 P61		FAB+: 167
323 P19		CI+: 275, 277

108

TABLE 61

324 P16 P8 P9		ESI+: 216
46 P46		ESI+: 171
51 P51		CI+: 153
325 P48		ESI+: 222
326 P55		ESI+: 222
327 P32		APCI+: 213
328 P8		ESI+: 316
47 P47		APCI+: 169
329 P9		ESI+: 186

109

TABLE 62

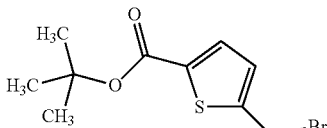
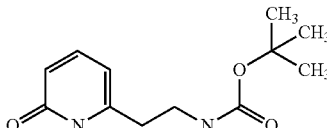
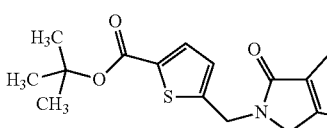
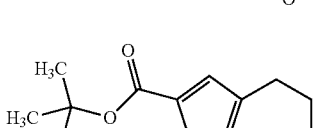
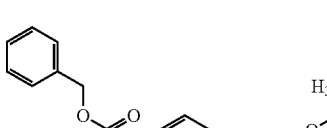
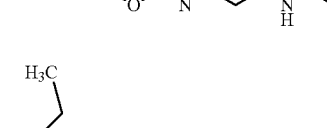
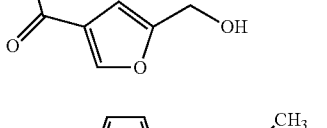
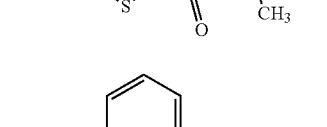
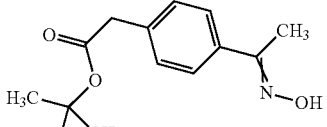
330 P19		APCI+: 279
331 P30		FAB+: 239
332 P55		FAB+: 343
333 P23		ESI+: 228
334 P57		ESI+: 387
335 P16		FAB+: 171
336 P32		ESI+: 214
337 P61 P51		EI+: 152

TABLE 63

338 P61		EI+: 249
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TABLE 63-continued


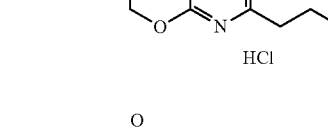
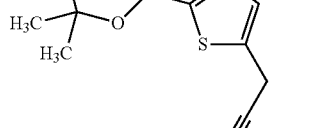
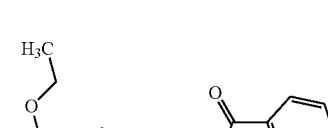
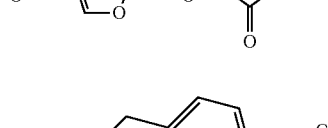
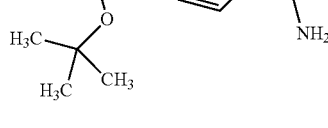
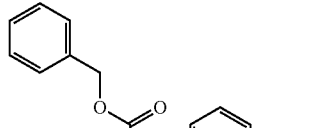
339 P26		ESI+: 287
340 P48		ESI+: 214
341 P8		APCI-: 314
342 P51		FAB+: 236
343 P16		FAB-: 199
344 P56		FAB+: 386

TABLE 64

345 P26		ESI+: 286
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111

TABLE 64-continued

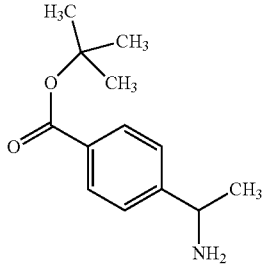
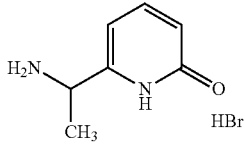
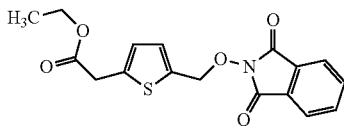
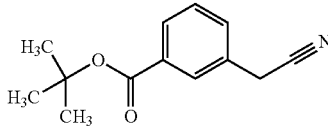
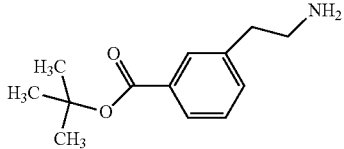
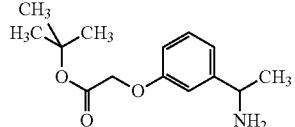
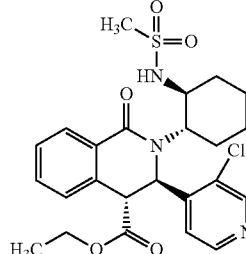
346 P61 P51		CI+: 222
54 P54		FAB+: 139
347 P8		NMR1: 1.19 (3H, t, J = 9.0 Hz), 3.90 (2H, s), 4.10 (1H, q, J = 9.0 Hz), 5.27 (2H, s), 6.87 (1H, d, J = 4.2 Hz), 7.10 (1H, d, J = 4.2 Hz), 7.82-7.93 (4H, m)
48 P48		CI+: 218
348 P23		EI+: 221

TABLE 65

349 P61 P51		FAB+: 252
350 P36		ESI+: 506 racemic mixture

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TABLE 65-continued

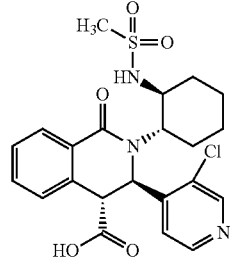
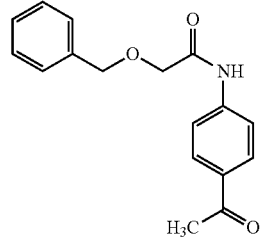
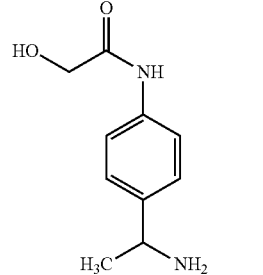
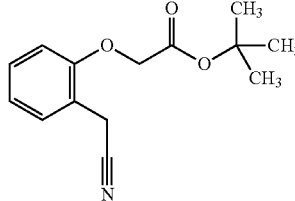
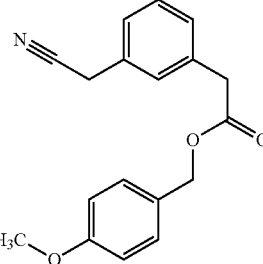
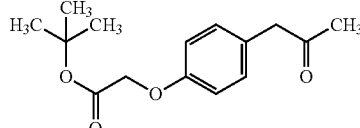
351 P38		ESI+: 478 racemic mixture
49 P49		CI+: 184
352 P61 P51		FAB+: 195

TABLE 66

56 P56		ESI+: 248
59 P59		ESI+: 300
353 P56		EI+: 264

113

TABLE 66-continued

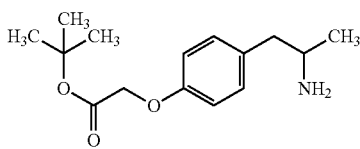
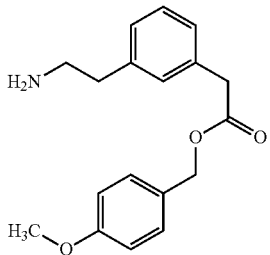
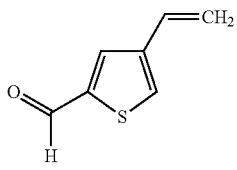
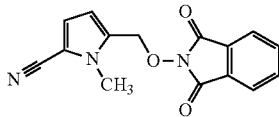
354 P61 P51		CI+: 266
355 P23		ESI+: 296
45 P45		NMR1: 5.31 (1H, d, J = 8.2 Hz), 5.79 (1H, d, J = 13.3 Hz), 6.75 (1H, dd, J = 13.3, 8.2 Hz), 8.07 (1H, s), 8.25 (1H, s), 9.92 (1H, s)

TABLE 67

356 P8		NMR1: 3.92 (3H, s), 5.22 (2H, s), 6.35 (1H, d, J = 3.0 Hz), 6.85 (1H, d, J = 3.0 Hz), 7.82-7.88 (4H, m)
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114

TABLE 67-continued

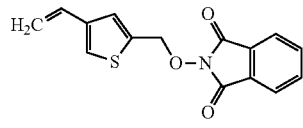
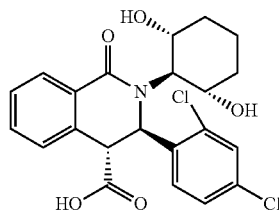
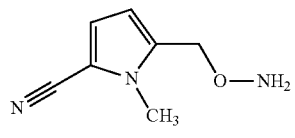
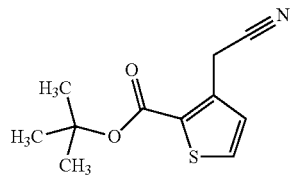
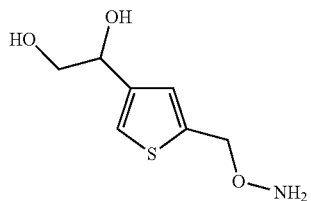
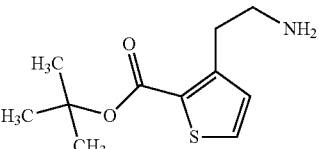
357 P16 P8		NMR1: 5.17 (1H, d, J = 8.1 Hz), 5.62 (2H, d, J = 13.2 Hz), 6.66 (1H, dd, J = 13.2, 8.1 Hz), 7.50 (1H, s), 7.58 (1H, s), 7.83-7.89 (4H, m)
358 P33 P34		ESI+: 450 racemic mixture
359 P9		ESI+: 152
360 P48		ESI+: 224

TABLE 68

361 P8 P9		NMR1: 3.38-3.52 (2H, m), 4.48-4.55 (1H, m), 4.65 (2H, s), 4.66-4.71 (1H, s), 5.15 (1H, d, J = 3.9 Hz), 6.08 (2H, s), 6.98 (1H, s), 7.22 (1H, s)
362 P23		ESI+: 228

115

TABLE 68-continued

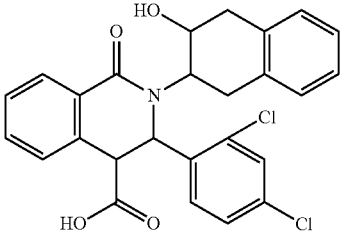
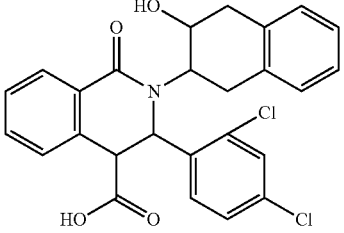
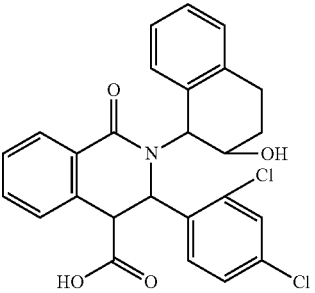
363	P33 P34		ESI-: 480	diastereomer of PEx364, racemic mixture, 1',2'-trans, 3,4-trans
364	P33 P34		ESI+: 482	diastereomer of PEx363, racemic mixture, 1',2'-trans, 3,4-trans
365	P33 P34		ESI-: 480	diastereomer of PEx366, racemic mixture, 1',2'-trans, 3,4-trans

TABLE 69

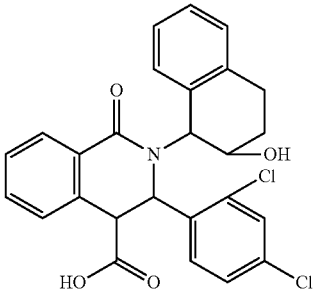
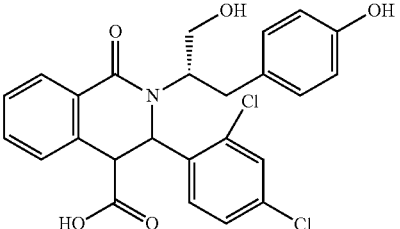
366	P33 P34		ESI+: 482	diastereomer of PEx365, racemic mixture, 1',2'-trans, 3,4-trans
367	P33 P34		ESI+: 486	

TABLE 69-continued

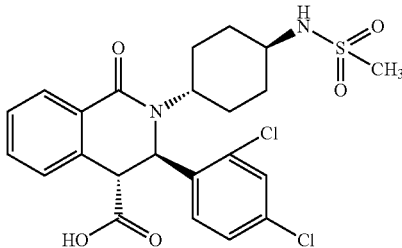
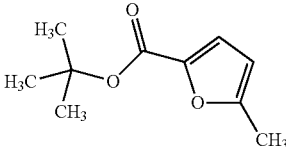
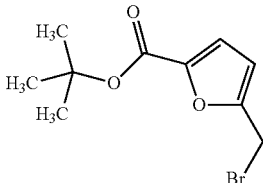
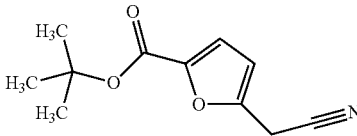
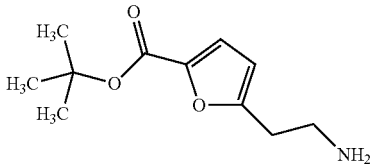
368	P33		ESI+: 511 racemic mixture
60	P60		EI+: 182
369	P19		EI+: 260, 262
370	P48		ESI-: 206
371	P23		ESI+: 212

TABLE 70

50

TABLE 70-continued

Ex	Structure	Note
60		
61		

119

TABLE 70-continued

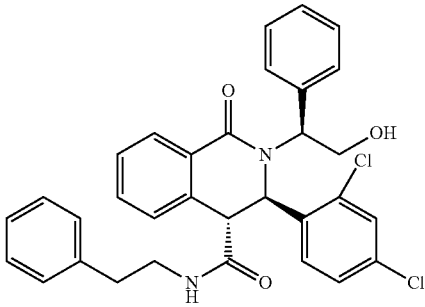
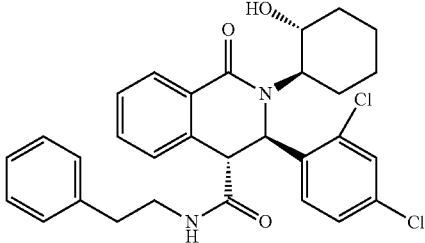
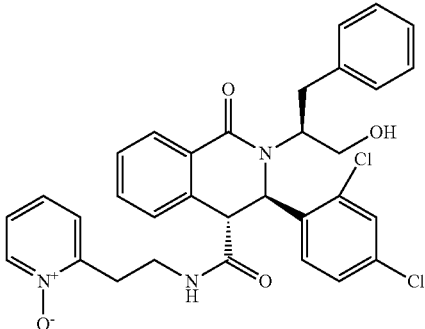
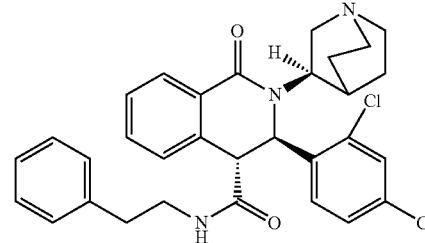
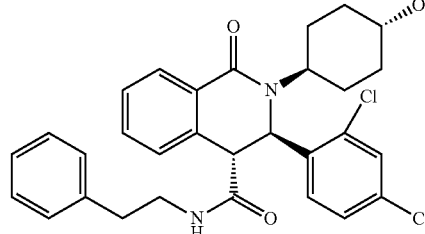
Ex	Structure	Note
62		
63		racemic mixture
64		

TABLE 71

65		
66		racemic mixture

120

TABLE 71-continued

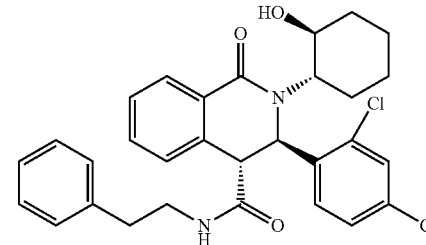
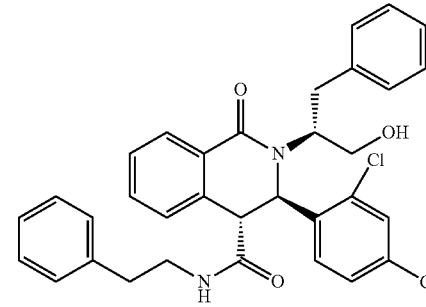
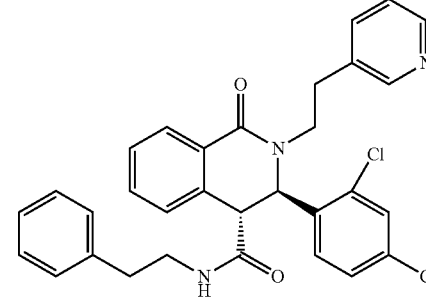
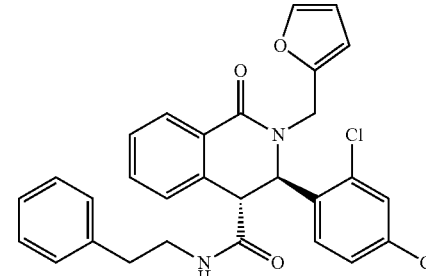
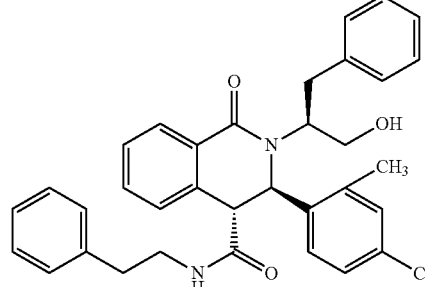
67		racemic mixture
68		
69		racemic mixture

TABLE 72

70		racemic mixture
71		

121

TABLE 72-continued

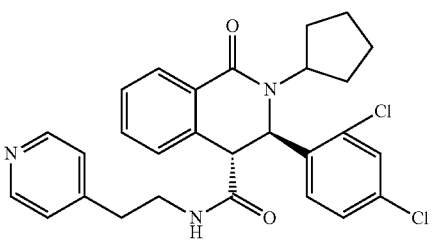
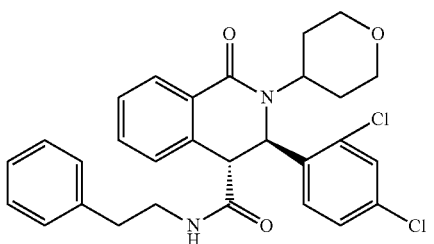
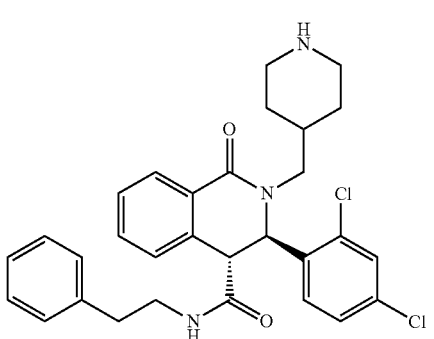
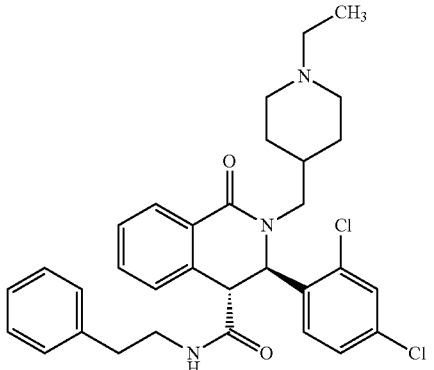
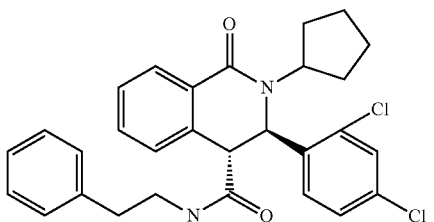
72		racemic mixture
73		racemic mixture
74		racemic mixture

TABLE 73

75		racemic mixture
1		racemic mixture

122

TABLE 73-continued

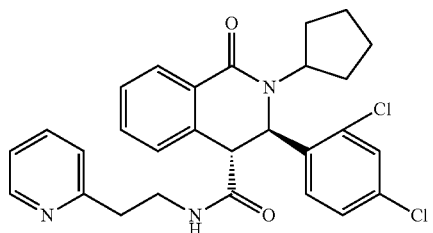
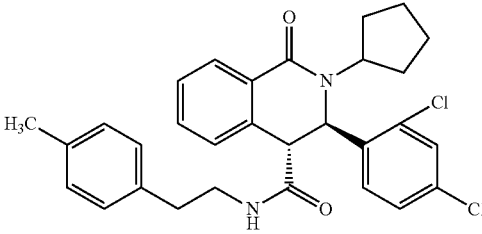
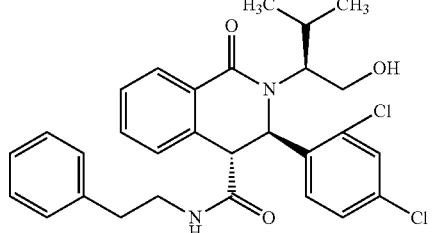
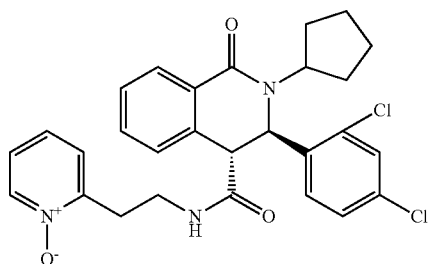
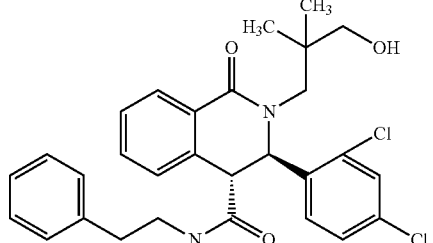
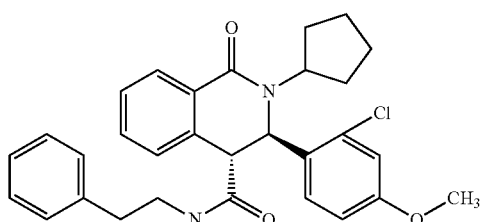
76		racemic mixture
77		racemic mixture
78		

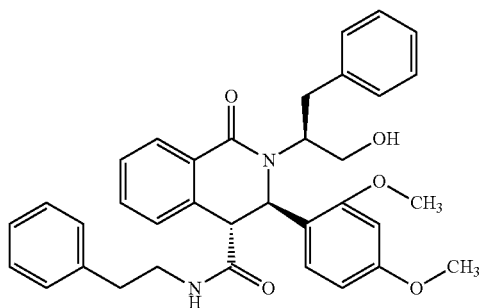
TABLE 74

3		racemic mixture
79		racemic mixture
80		racemic mixture

123

TABLE 74-continued

81



82

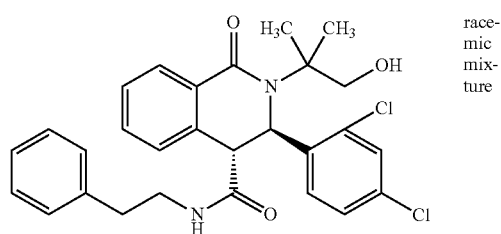
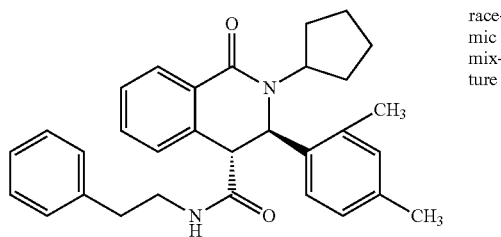
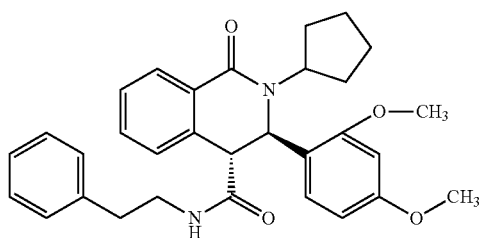


TABLE 75

83



84



85

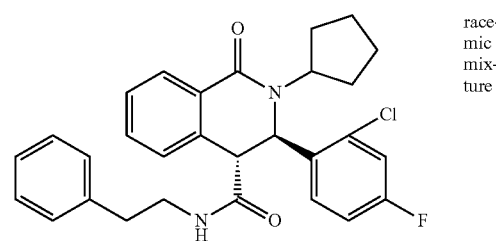
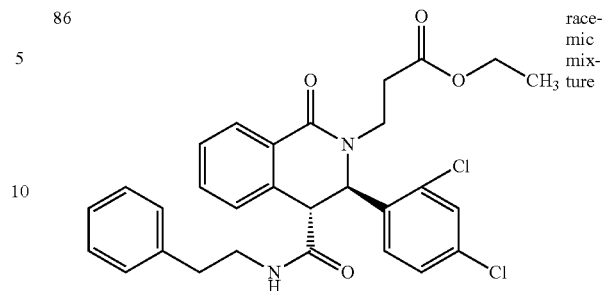
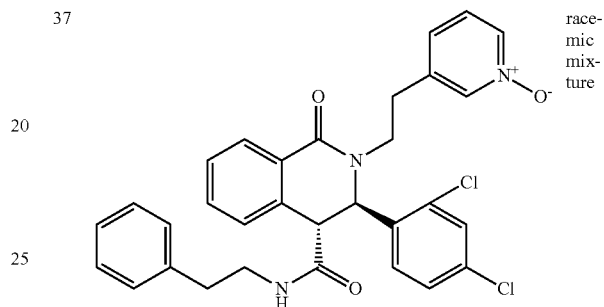
**124**

TABLE 75-continued

86



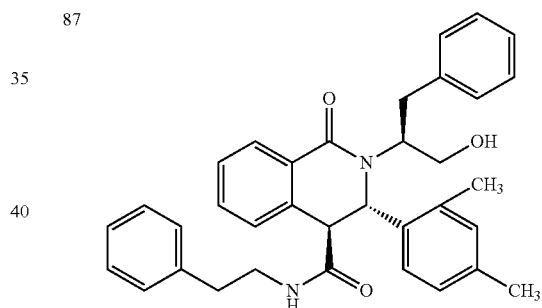
37



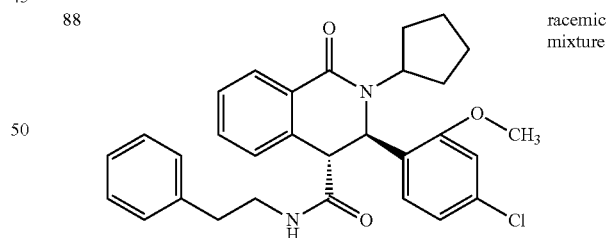
30

TABLE 76

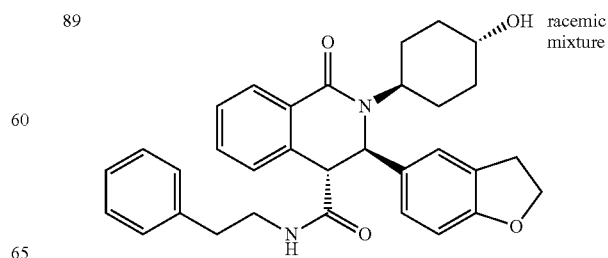
87



88



89



125

TABLE 76-continued

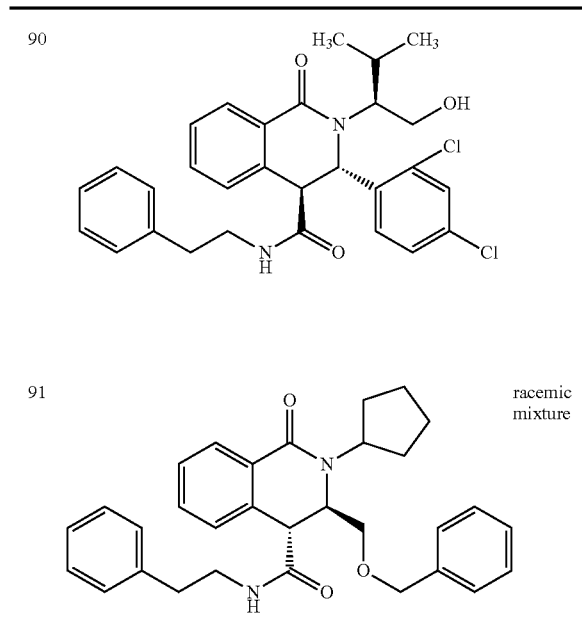


TABLE 77

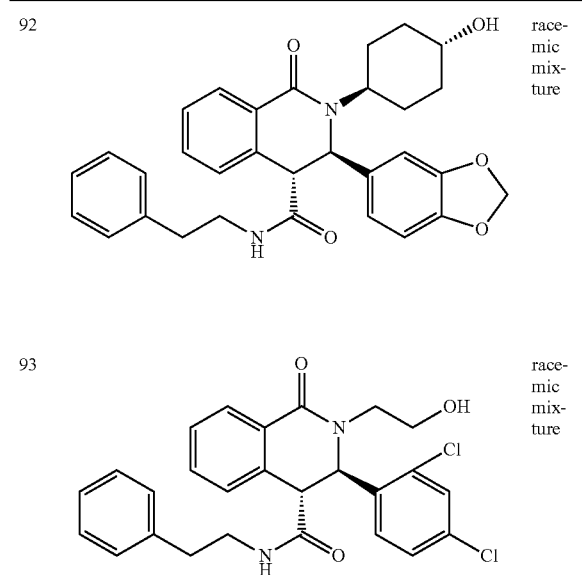
**126**

TABLE 77-continued

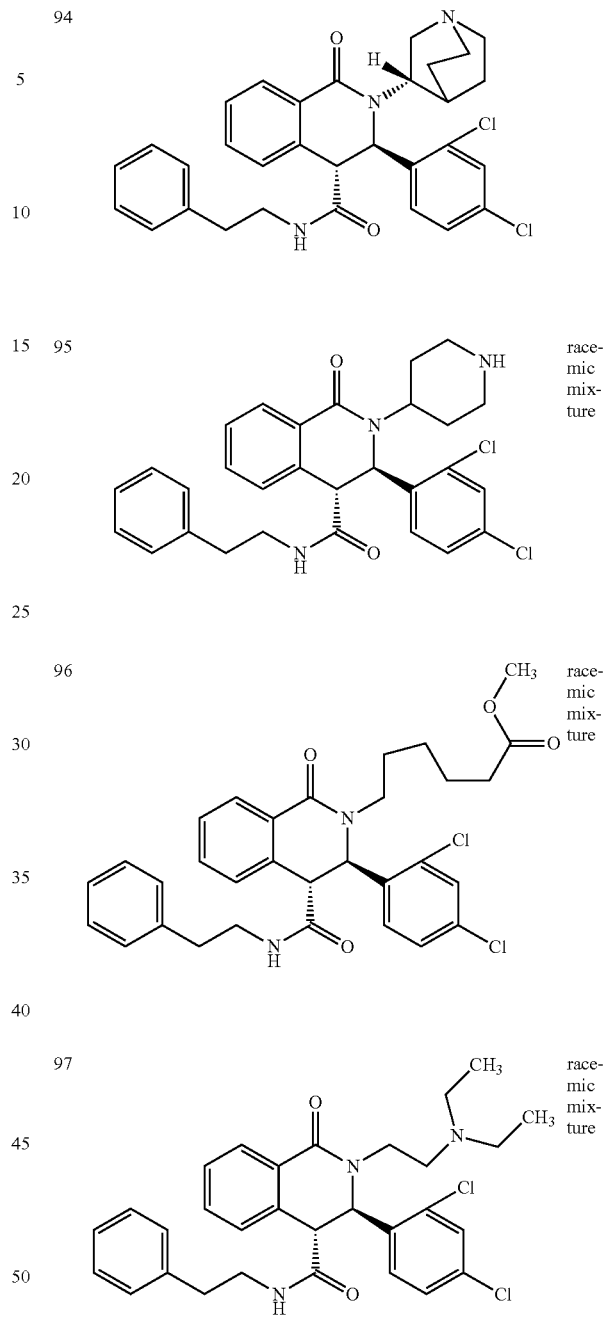


TABLE 78

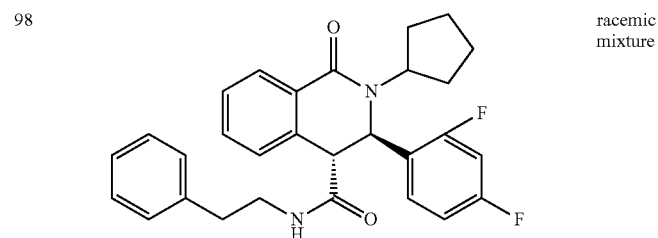
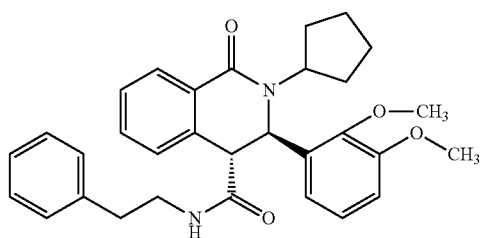
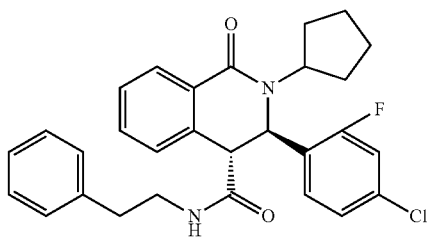


TABLE 78-continued

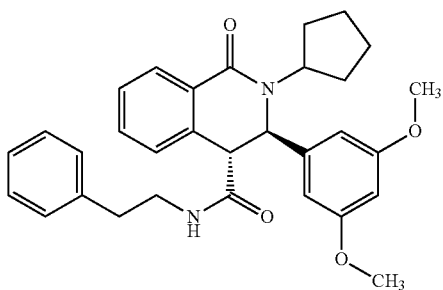
99

racemic
mixture

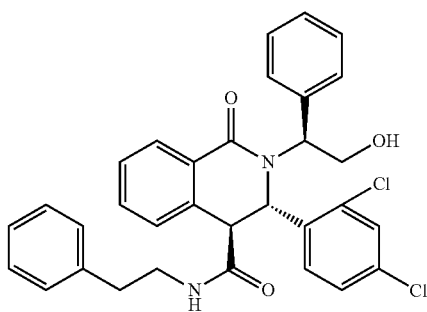
100

racemic
mixture

101

racemic
mixture

102



103

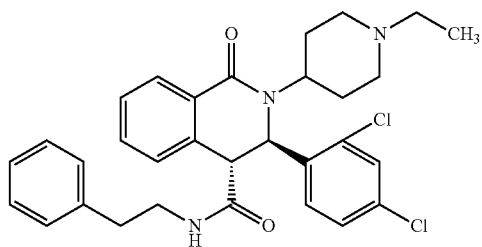
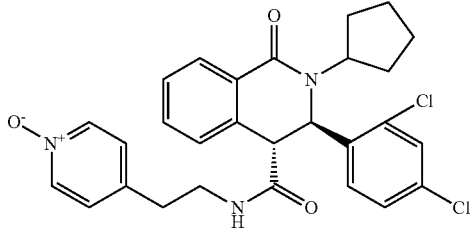
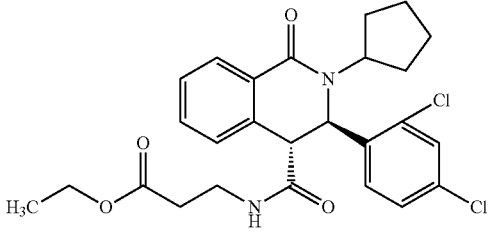
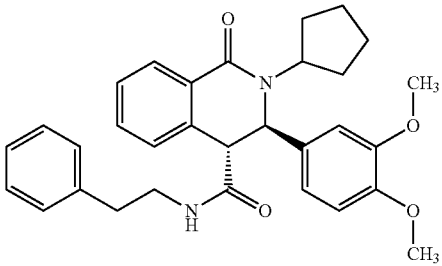
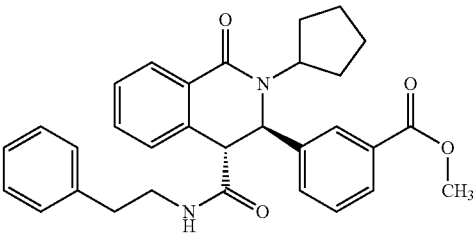
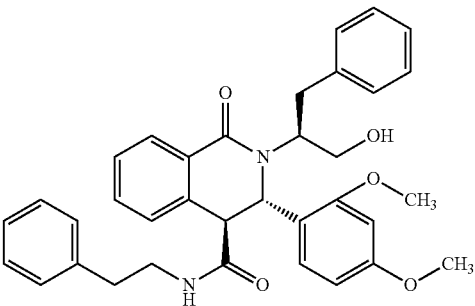
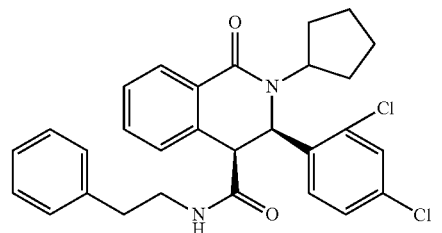
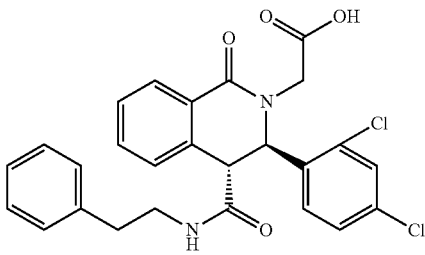
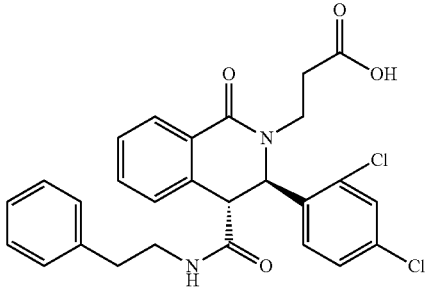
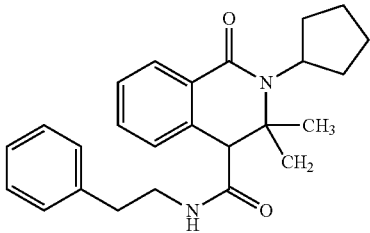
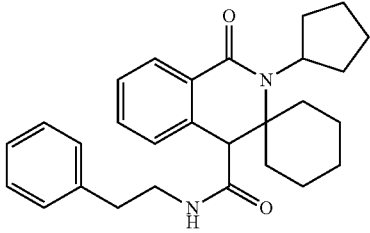
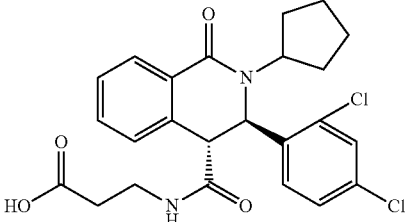
racemic
mixture

TABLE 79

104		racemic mixture
105		racemic mixture
106		racemic mixture
107		racemic mixture
108		
2		racemic mixture

131
TABLE 80

109		racemic mixture
39		racemic mixture
110		racemic mixture
111		racemic mixture
4		racemic mixture

132
TABLE 81

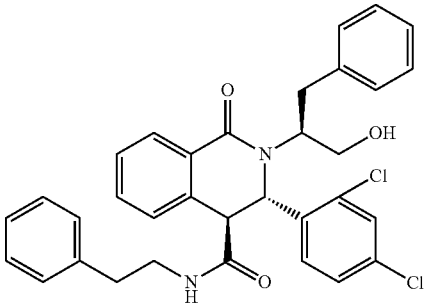
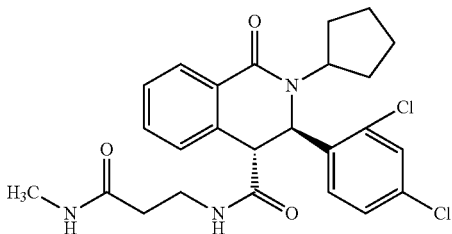
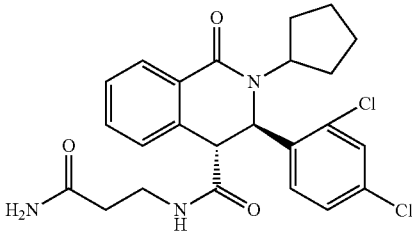
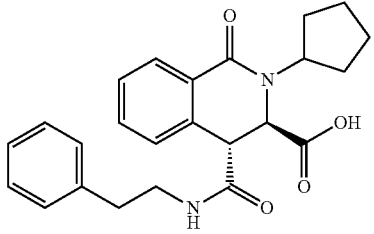
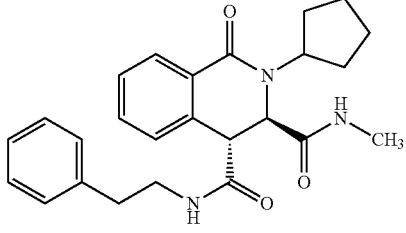
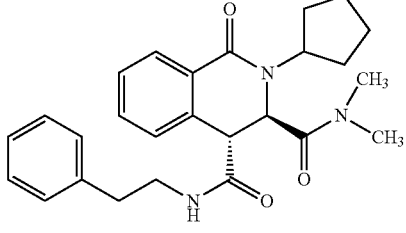
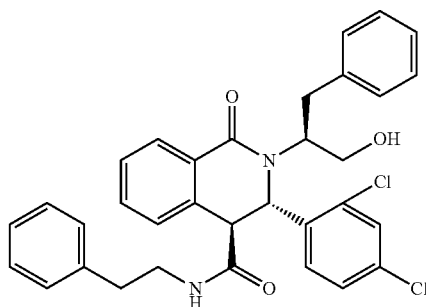
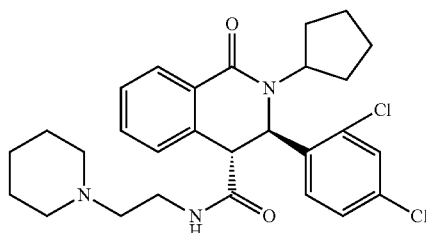
112		
5		
10		
15		
113		racemic mixture
20		
25		
114		racemic mixture
30		
35		
115		racemic mixture
40		
45		
116		racemic mixture
50		
55		
117		racemic mixture
60		
65		

TABLE 82

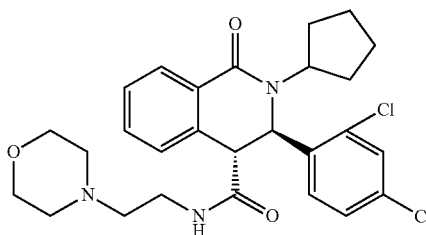
118



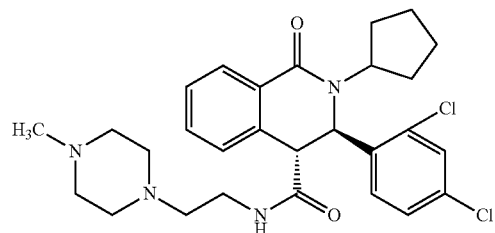
119

racemic
mixture

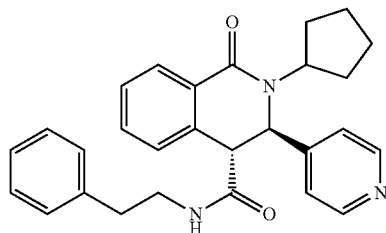
120

racemic
mixture

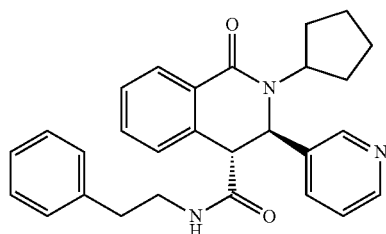
121

racemic
mixture

122

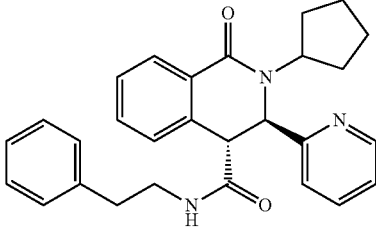
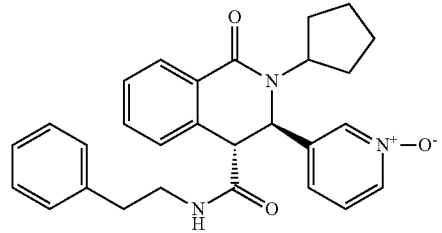
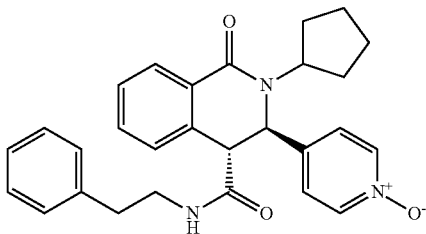
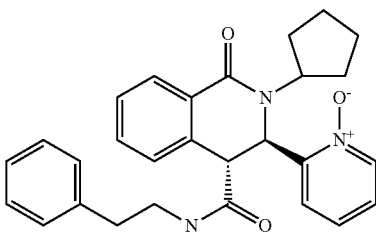
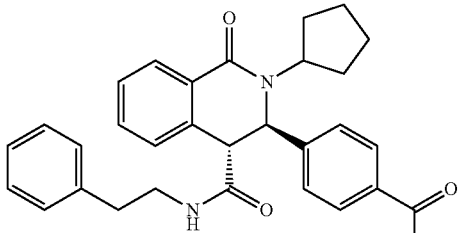
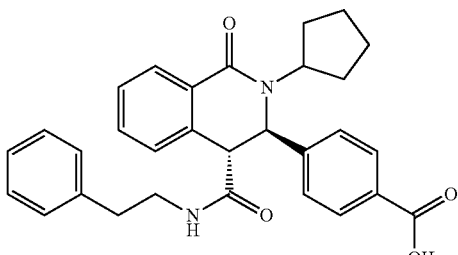
racemic
mixture

123

racemic
mixture

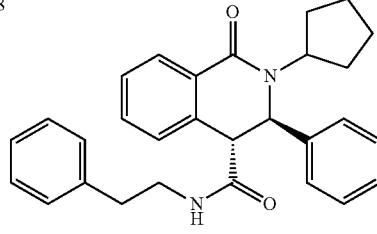
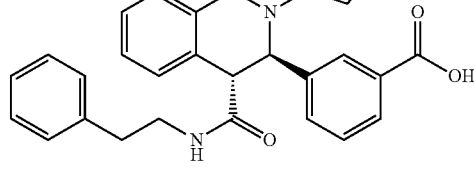
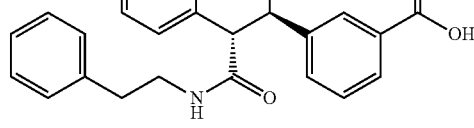
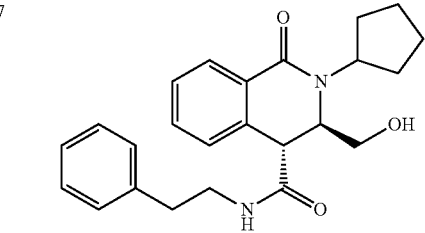
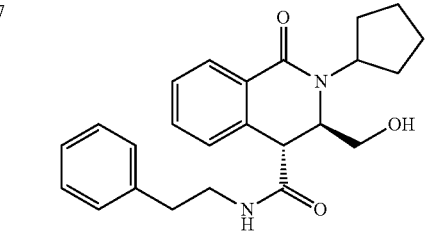
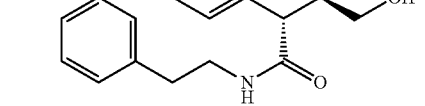
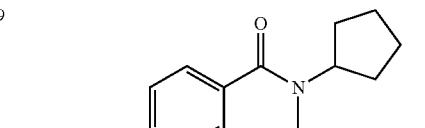
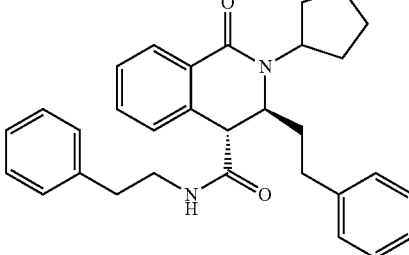
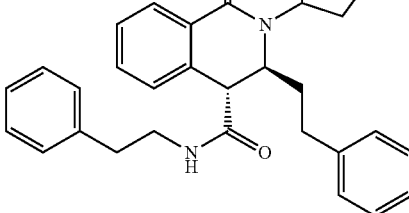
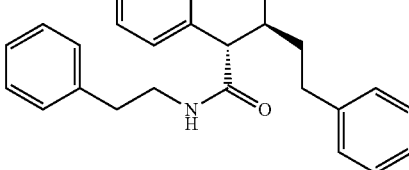
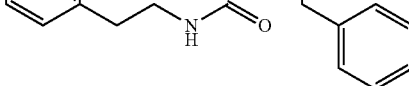
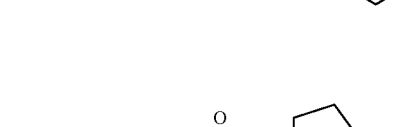
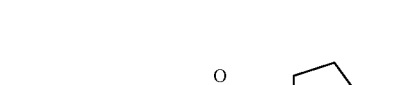
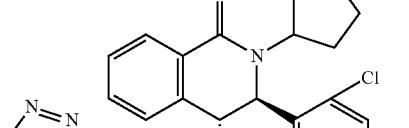
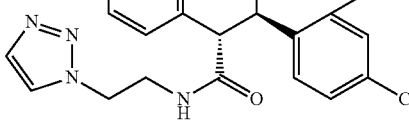
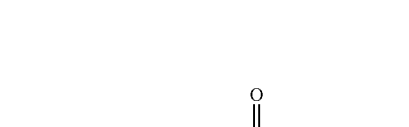
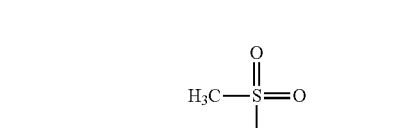
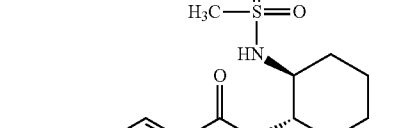
135

TABLE 83

124		racemic mixture
36		racemic mixture
125		racemic mixture
126		racemic mixture
127		racemic mixture
38		racemic mixture

136

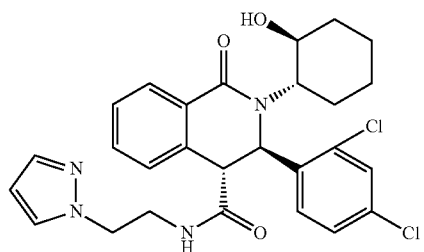
TABLE 84

128		racemic mixture
5		
10		
15		racemic mixture
7		
20		
25		
129		racemic mixture
30		
35		
40		
130		racemic mixture
45		
50		
10		
55		racemic mixture
60		
65		

137

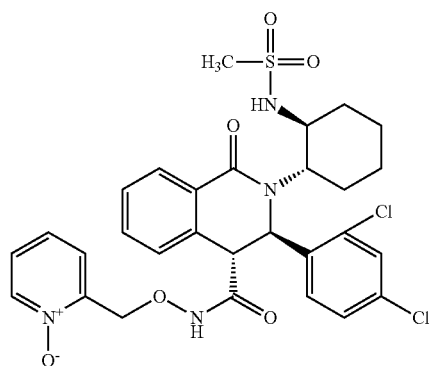
TABLE 85

131



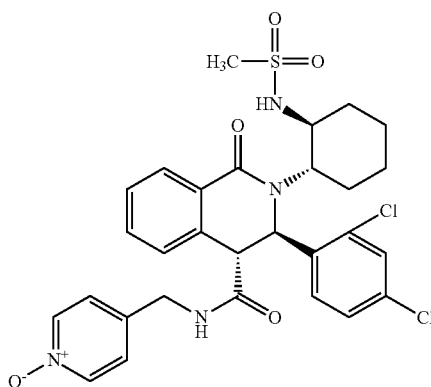
racemic mixture

132



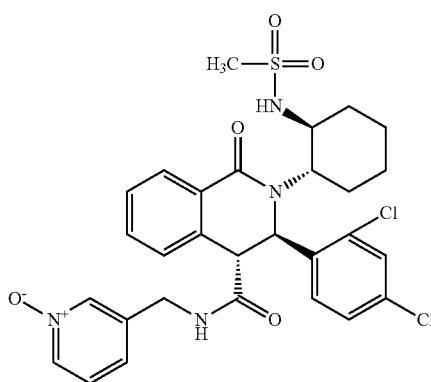
racemic mixture

133



racemic mixture

134



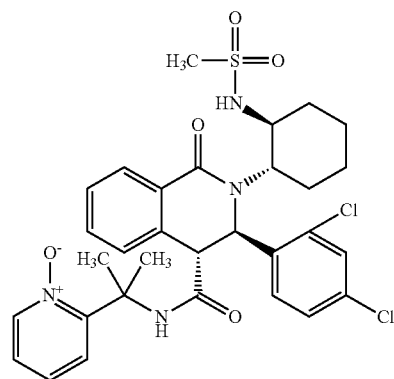
racemic mixture

138

TABLE 86

135

5



racemic mixture

10

15

20

136

25

30

35

137

40

45

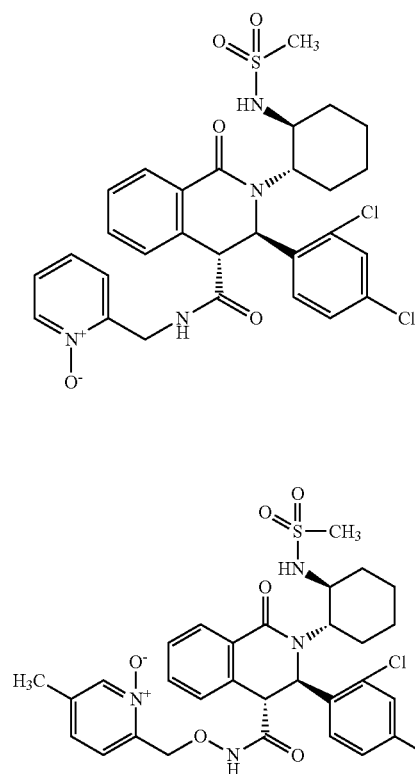
50

138

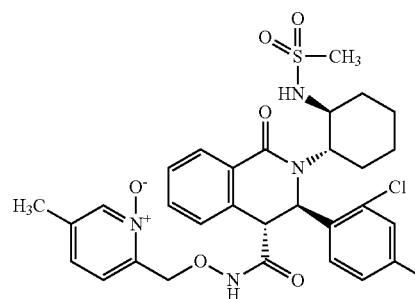
55

60

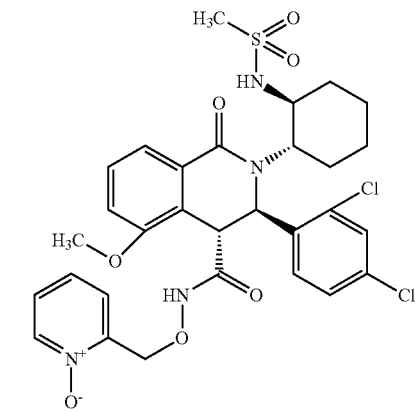
65



racemic mixture



racemic mixture

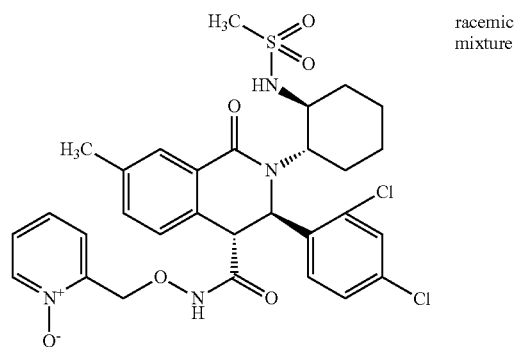


racemic mixture

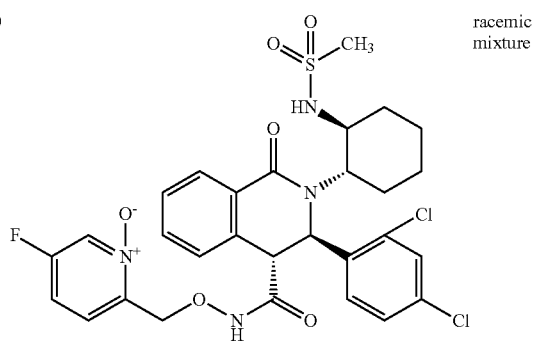
139

TABLE 87

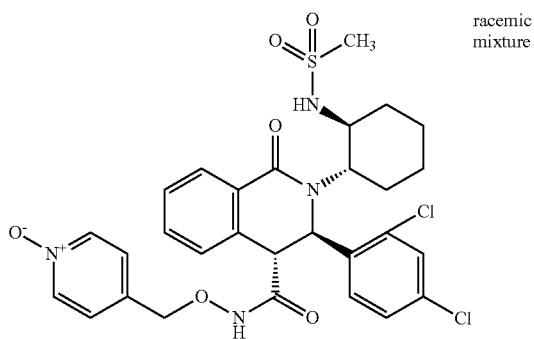
139



140



141



142

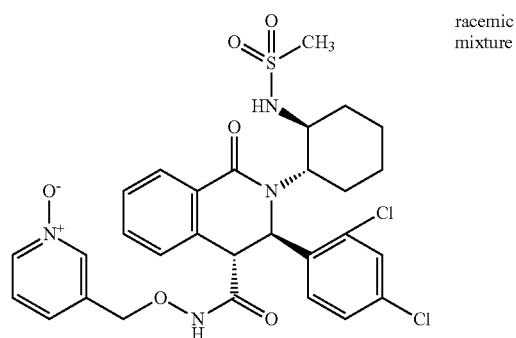
**140**

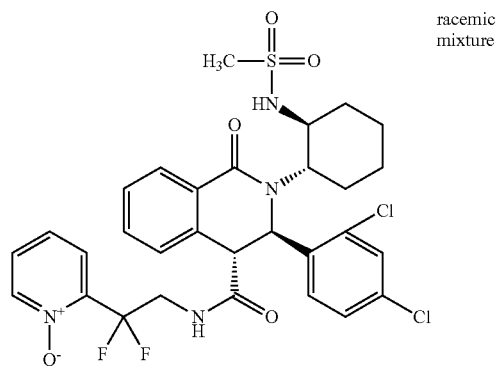
TABLE 88

143

5

10

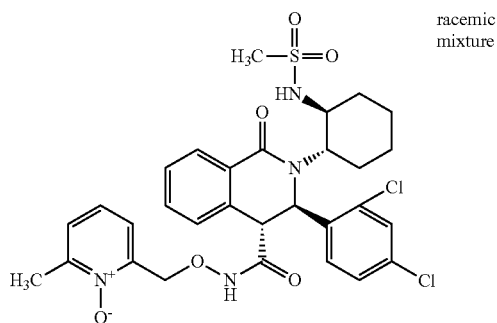
15



20 144

25

30

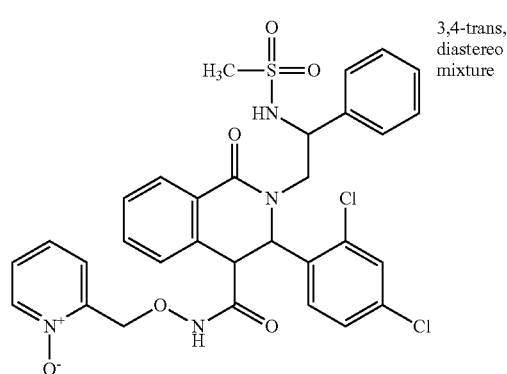


35 145

40

45

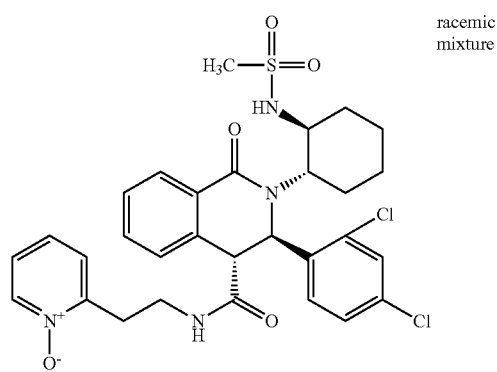
50



55 146

60

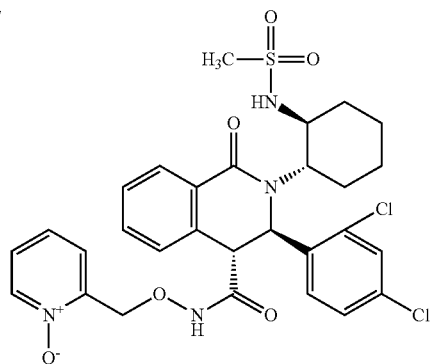
65



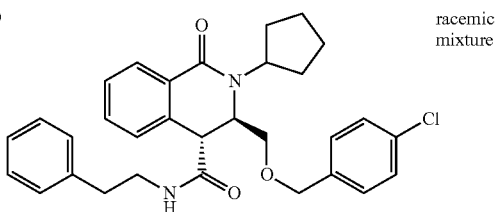
141

TABLE 89

147

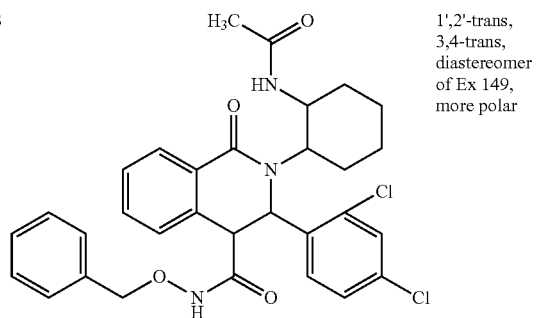


9



racemic mixture

148

1',2'-trans,
3,4-trans,
diastereomer
of Ex 149,
more polar

149

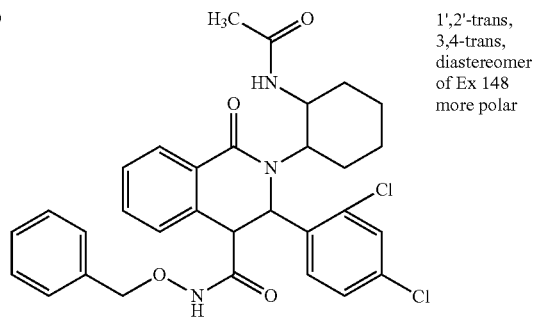
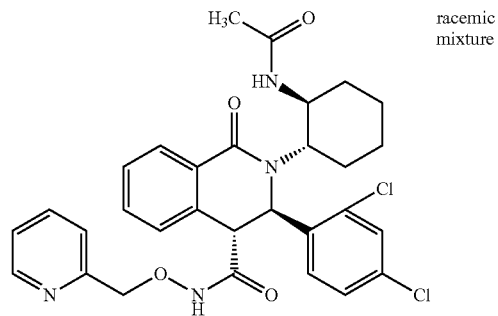
1',2'-trans,
3,4-trans,
diastereomer
of Ex 148
more polar

TABLE 90

11



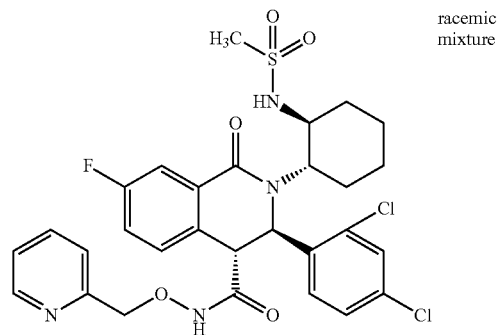
racemic mixture

142

TABLE 90-continued

150

5



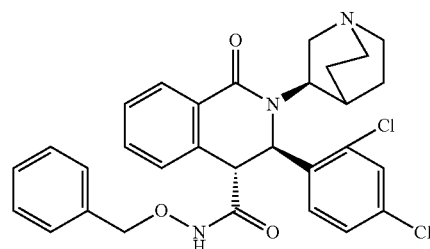
racemic mixture

10

15

151

20

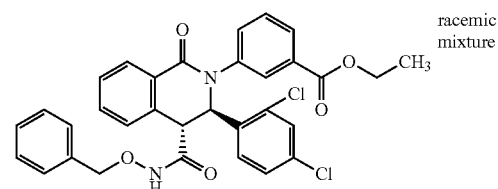


25

30

152

35

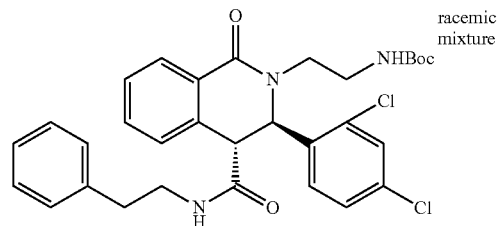


racemic mixture

40

153

45



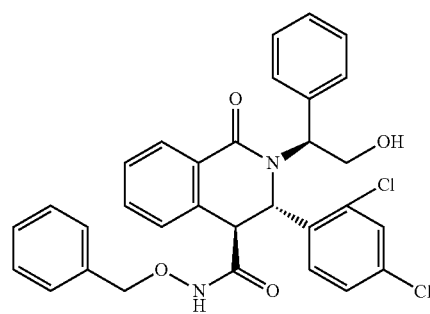
racemic mixture

50

TABLE 91

154

55



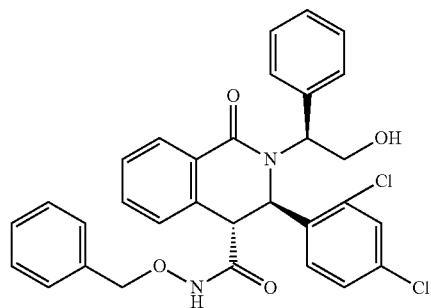
60

65

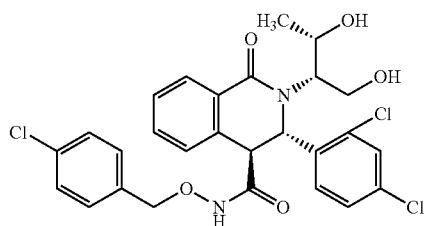
143

TABLE 91-continued

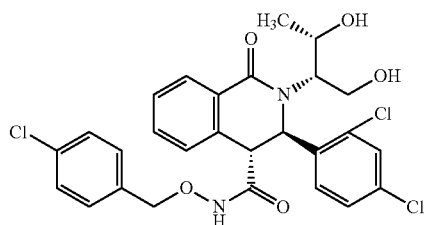
155



156



157



158

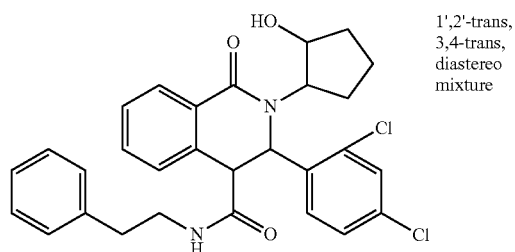
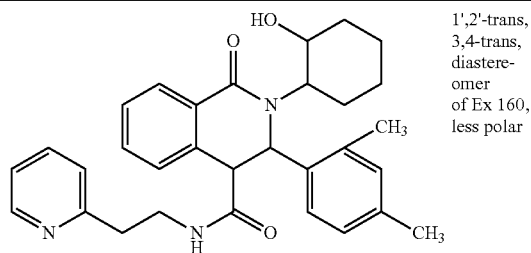
1',2'-trans,
3,4-trans,
diastereo-
mixture

TABLE 92

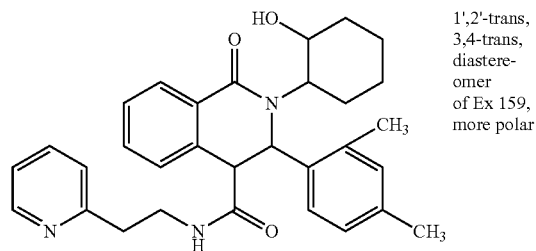
159

1',2'-trans,
3,4-trans,
diastereo-
mixture
of Ex 160,
less polar

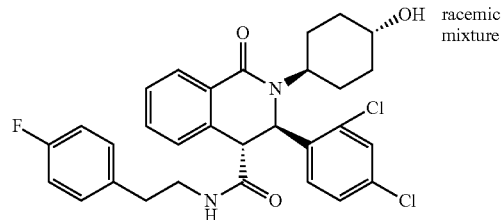
144

TABLE 92-continued

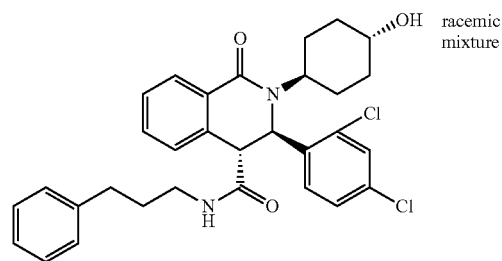
160

1',2'-trans,
3,4-trans,
diastereo-
mixture
of Ex 159,
more polar

161

racemic
mixture

162

racemic
mixture

163

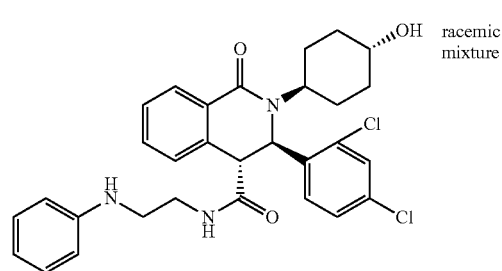
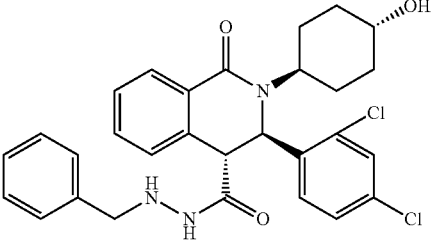
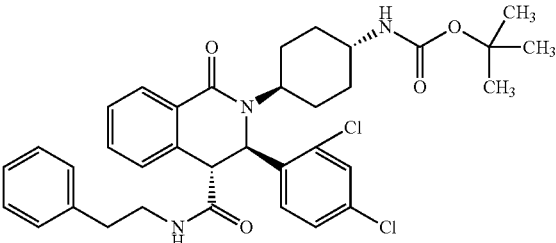
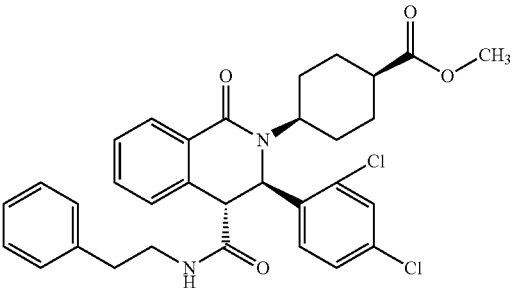
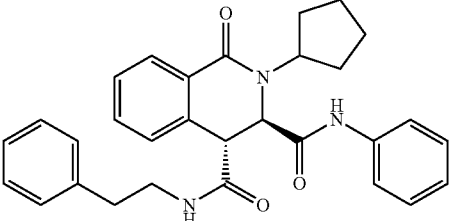
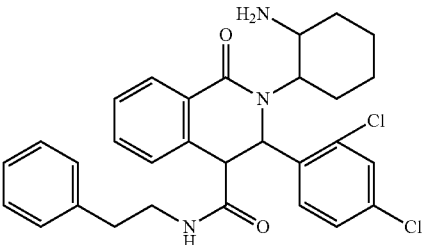
racemic
mixture

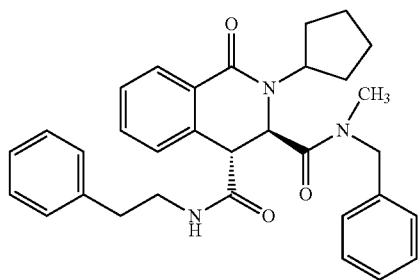
TABLE 93

164		racemic mixture
165		racemic mixture
166		racemic mixture
167		racemic mixture
168		

147

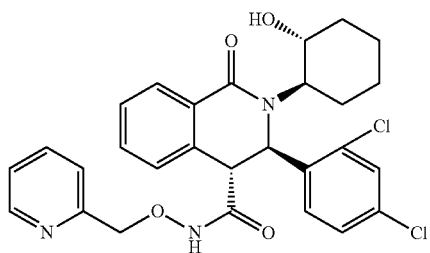
TABLE 94

169



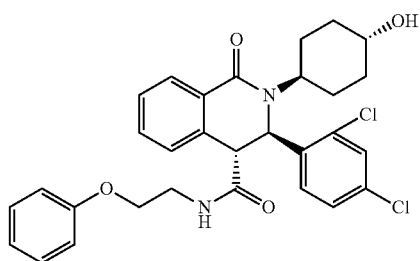
racemic mixture

170



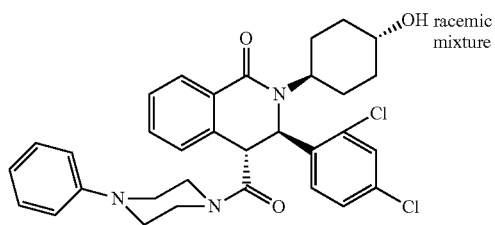
racemic mixture

171



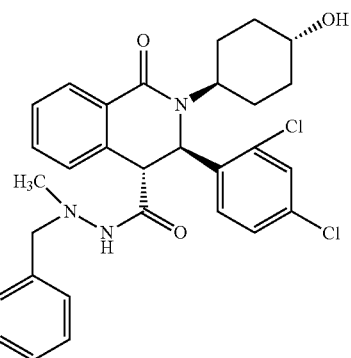
racemic mixture

172



racemic mixture

173

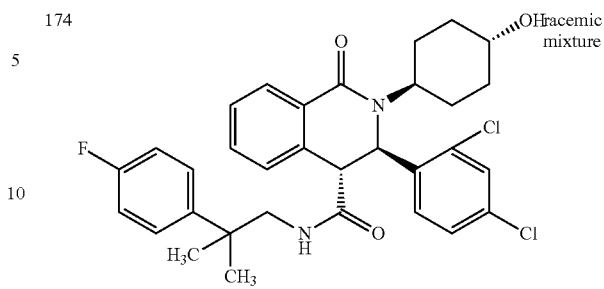


racemic mixture

148

TABLE 95

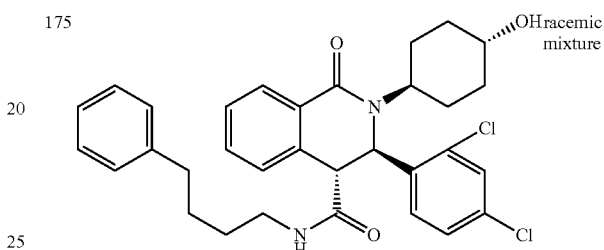
174



racemic mixture

15

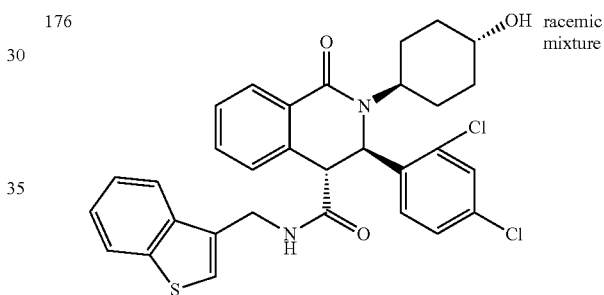
175



racemic mixture

25

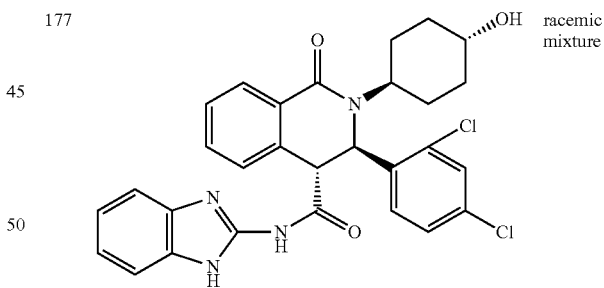
176



racemic mixture

40

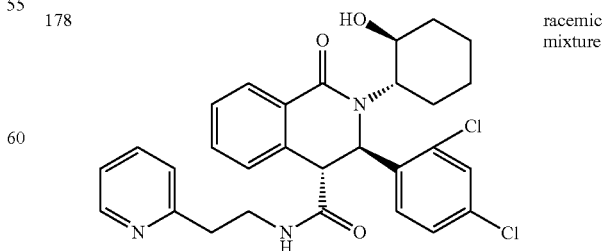
177



racemic mixture

55

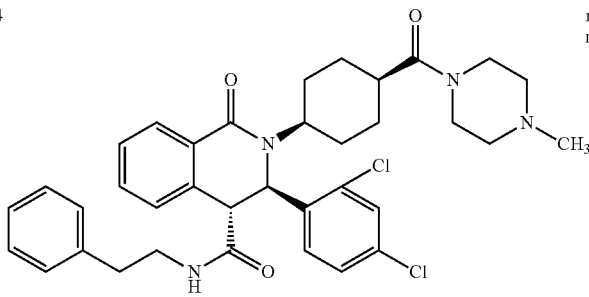
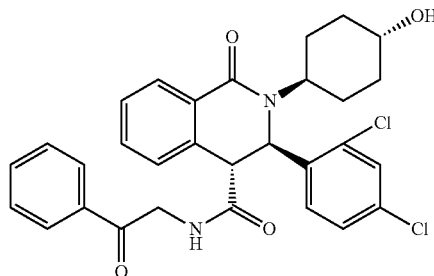
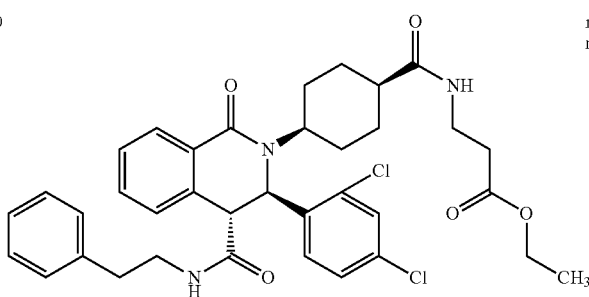
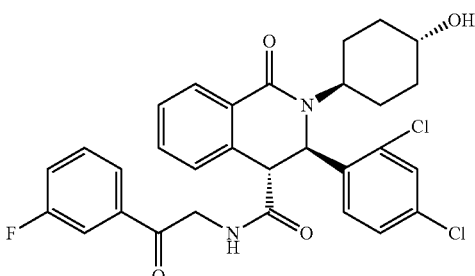
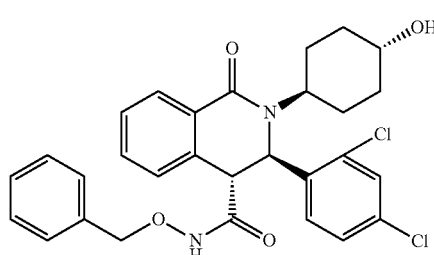
178



racemic mixture

65

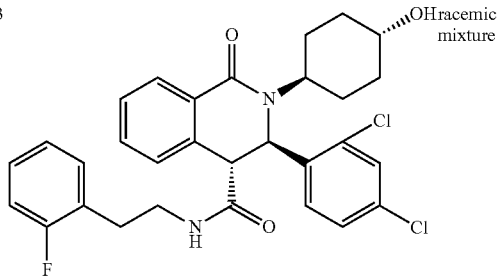
TABLE 96

34		racemic mixture
179		racemic mixture
180		racemic mixture
181		racemic mixture
182		racemic mixture

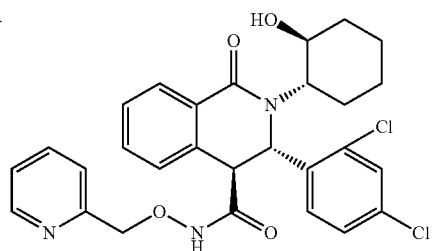
151

TABLE 97

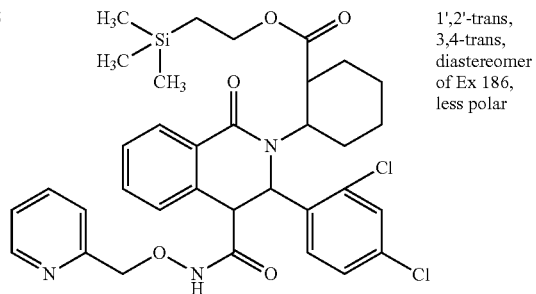
183



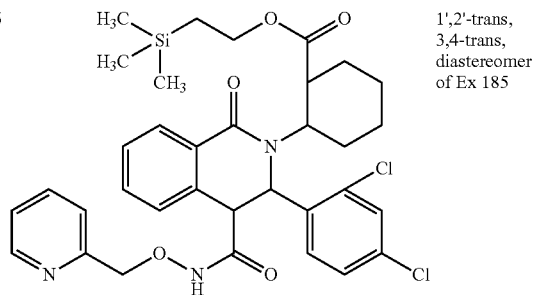
184



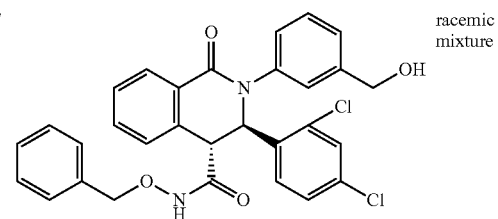
185



186



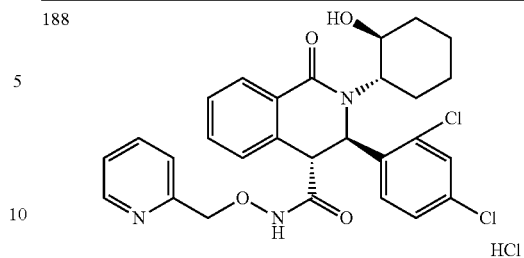
187



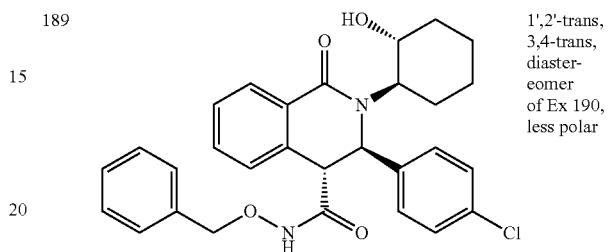
152

TABLE 98

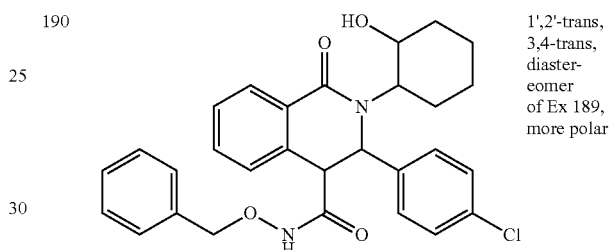
188



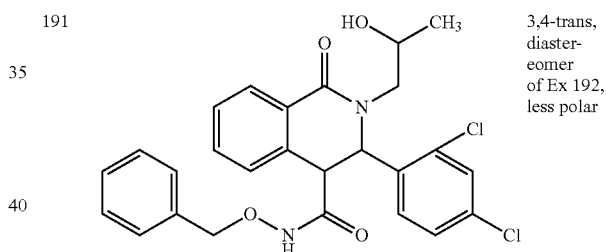
189



190



191



192

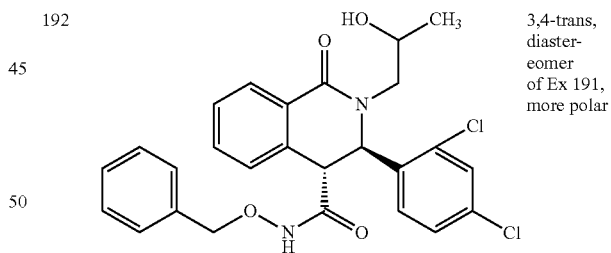
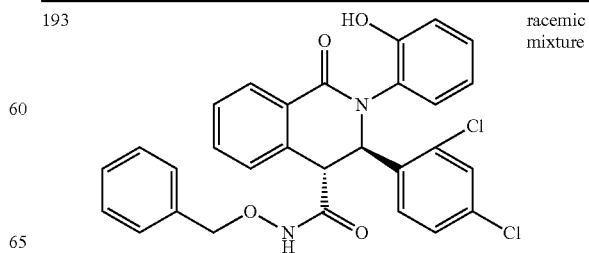


TABLE 99

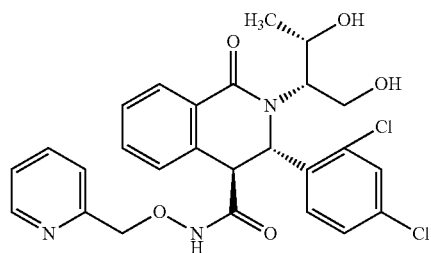
193



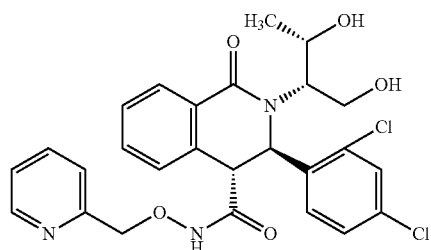
153

TABLE 99-continued

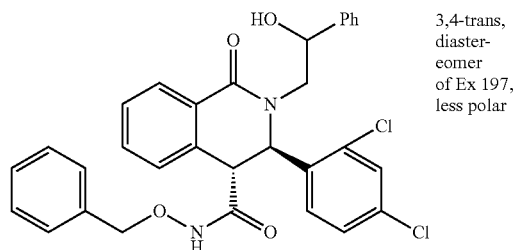
194



195



196



197

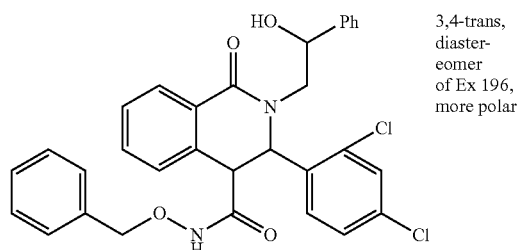
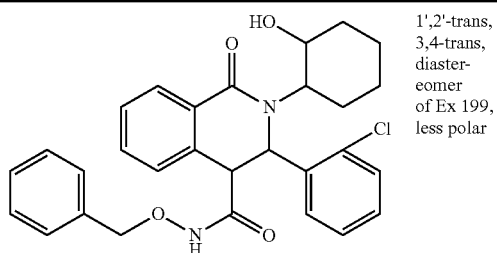


TABLE 100

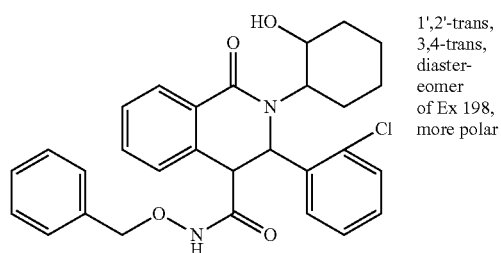
198



154

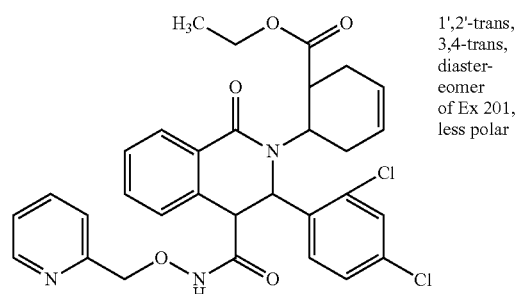
TABLE 100-continued

199

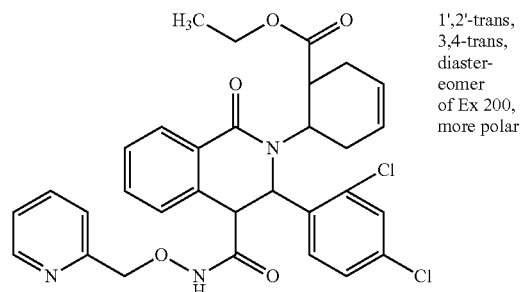


15

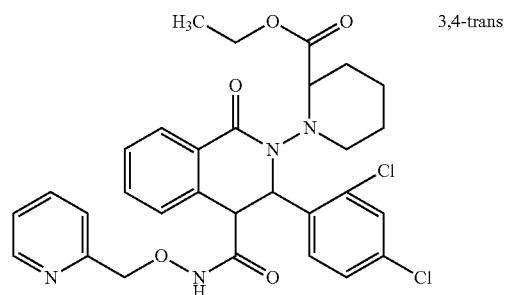
200



201



55



65

TABLE 101

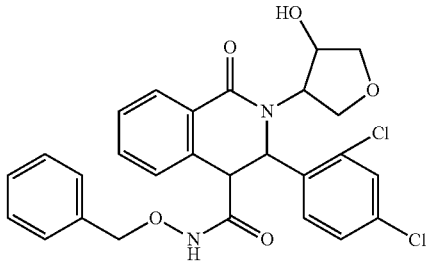
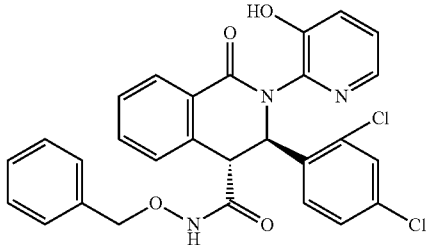
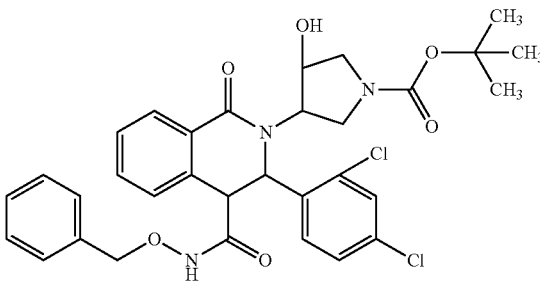
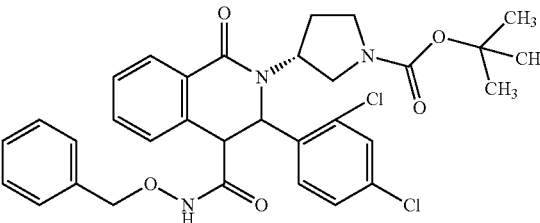
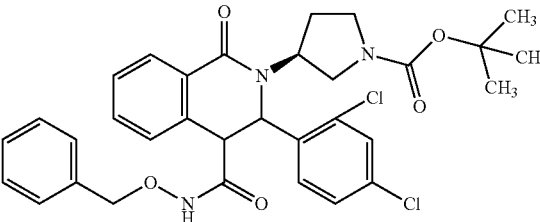
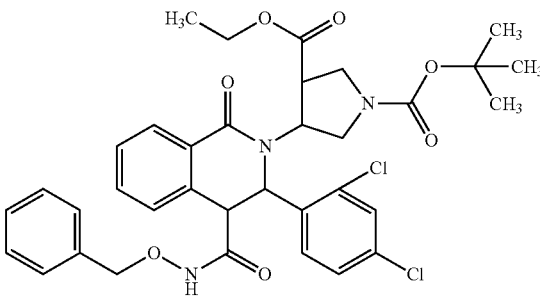
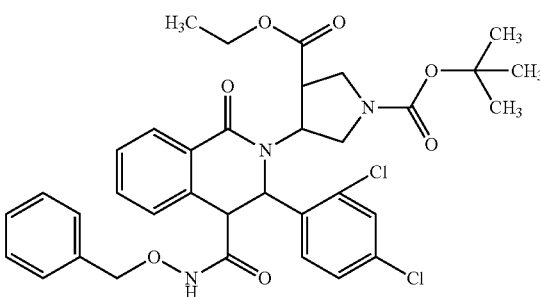
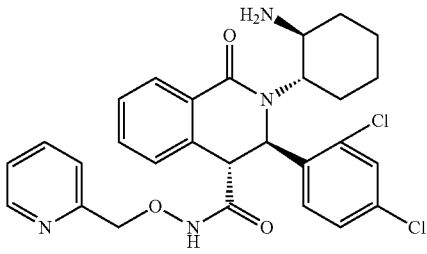
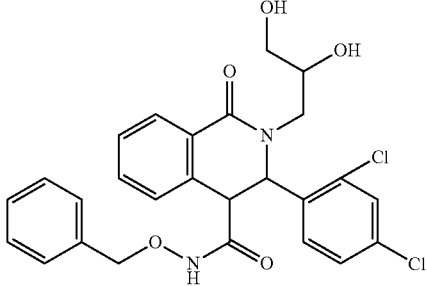
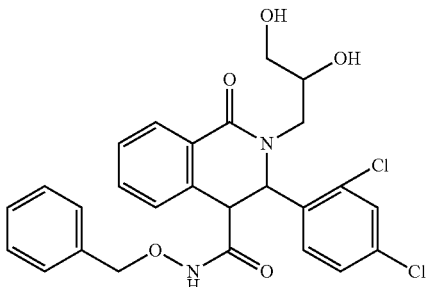
203		1',2'-trans, 3,4-trans, diastereomer of Ex 409
204		racemic mixture
205		1',2'-trans, 3,4-trans, distereo mixture
206		3,4-trans, distereo mixture
207		3,4-trans distereo mixture

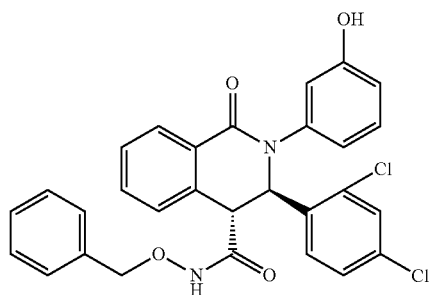
TABLE 102

208		1',2'-trans, 3,4-trans, distereomer of Ex 209
209		1',2'-trans, 3,4-trans, distereomer of Ex 208
210		racemic mixture
211		3,4-trans, diastereomer of Ex 212, less polar
212		3,4-trans, diastereomer of Ex 211, more polar

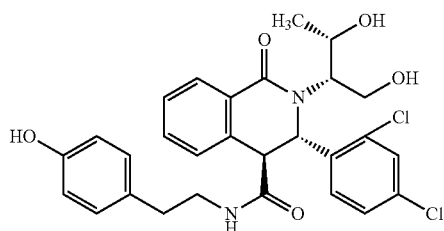
159

TABLE 103

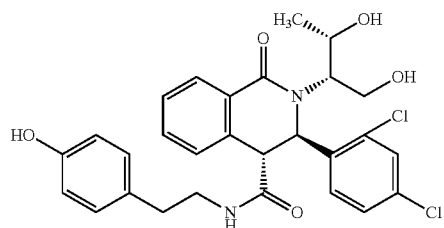
213



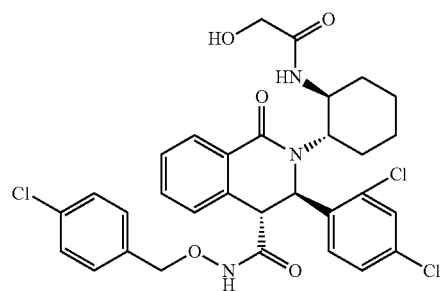
214



215



216



217

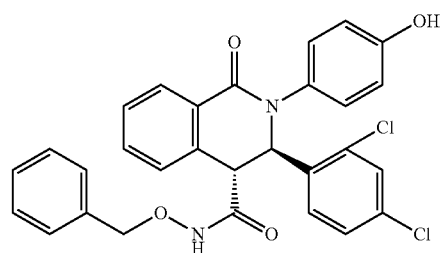
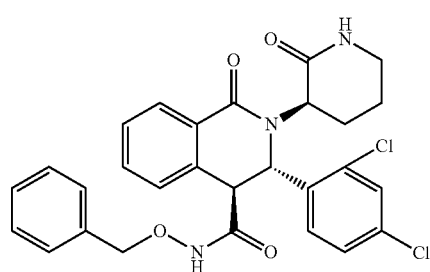
**160**

TABLE 104

218

5



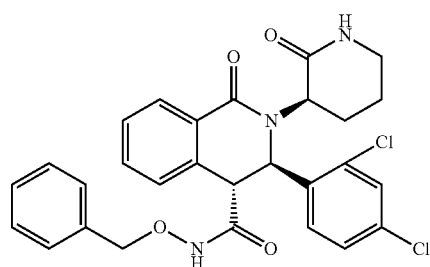
10

15

219

20

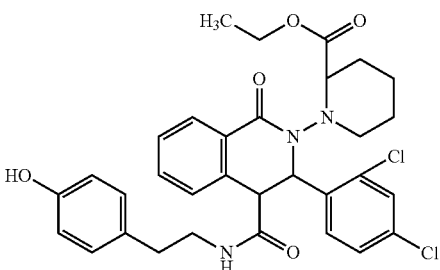
25



30

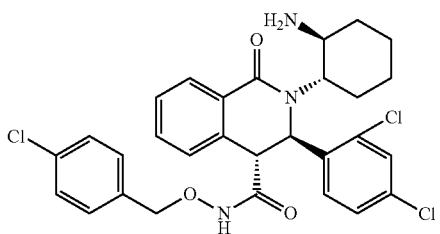
35

40



45

50

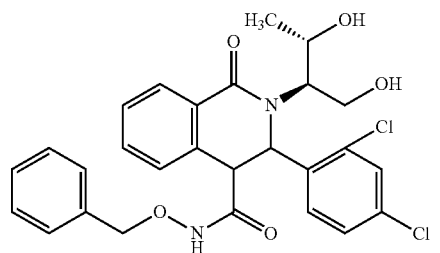


55

222

60

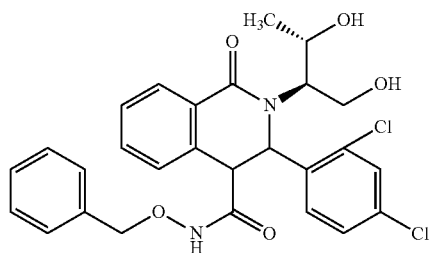
65



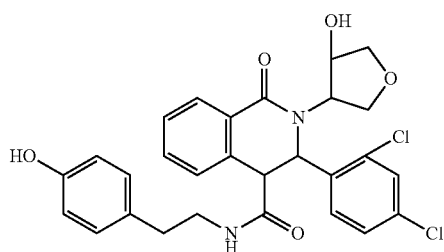
161

TABLE 105

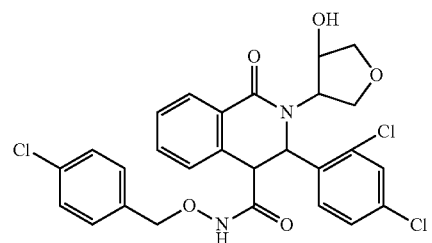
223

3,4-trans,
diaster-
eomer
of Ex
222,
more
polar

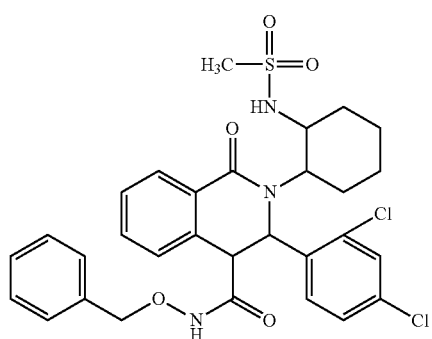
224

1',2'-
trans,
3,4-
trans

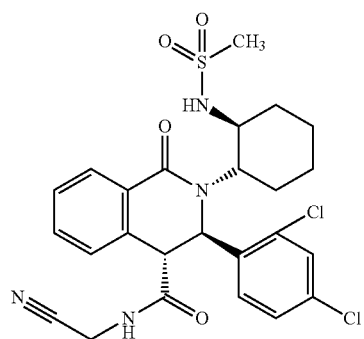
225

1',2'-
trans,
3,4-
trans

226

racemic
mixture,
1',2'-
cis,
3,4-
trans

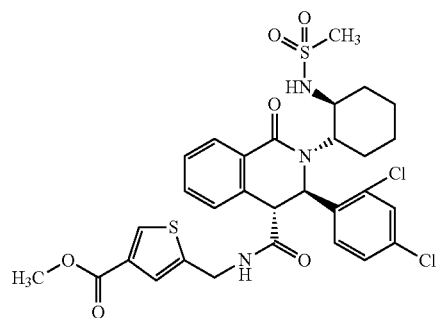
227

racemic
mixture

162

TABLE 106

228

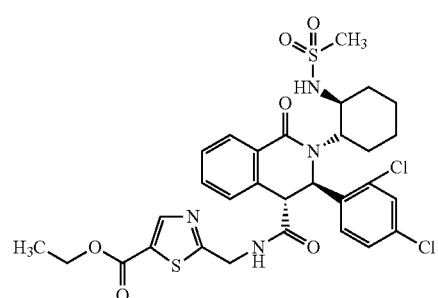
racemic
mixture

5

10

15

20 229

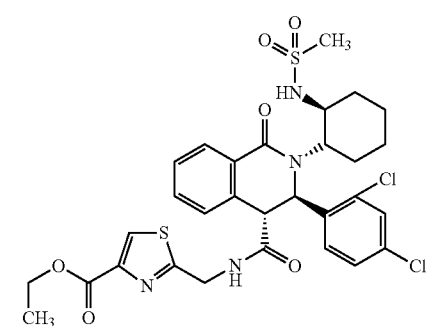
racemic
mixture

25

30

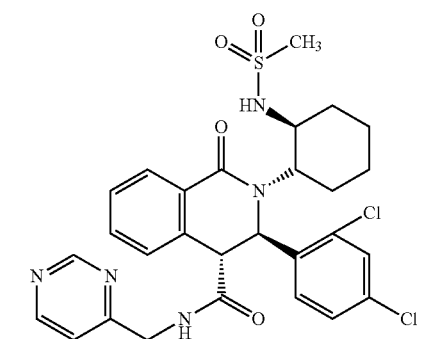
35

230

racemic
mixture

50

231

racemic
mixture

55

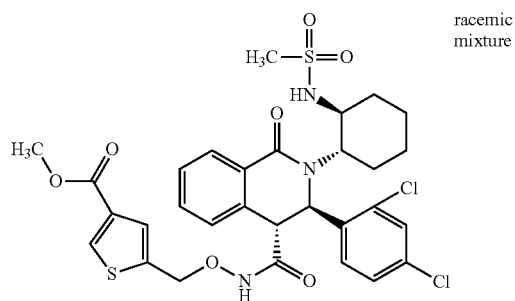
60

65

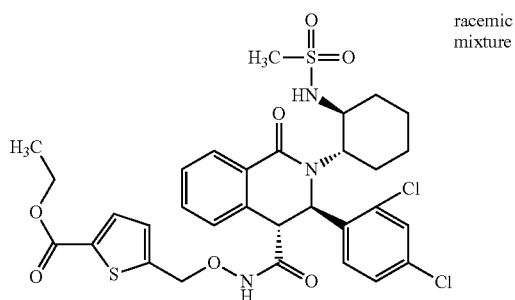
163

TABLE 107

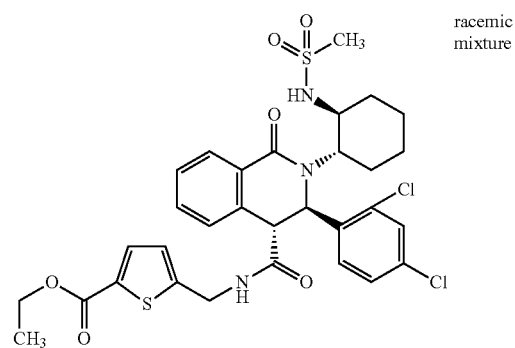
232



233



234



235

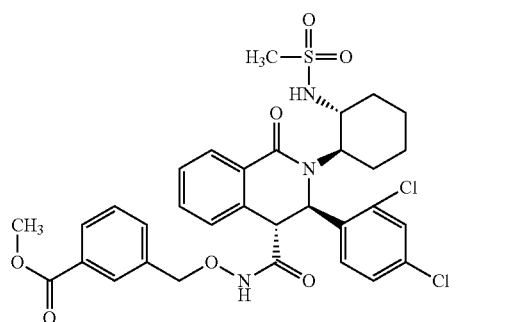
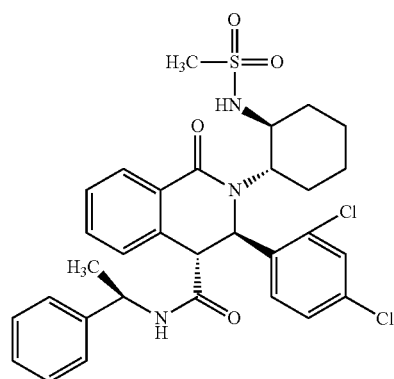
**164**

TABLE 108

236

5



10

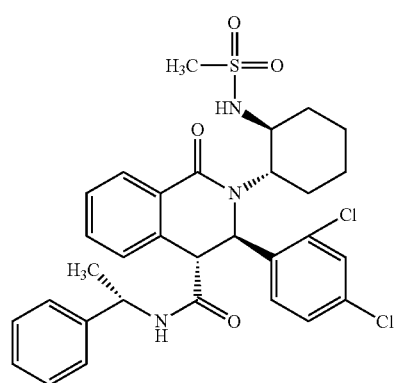
15

237

25

30

35

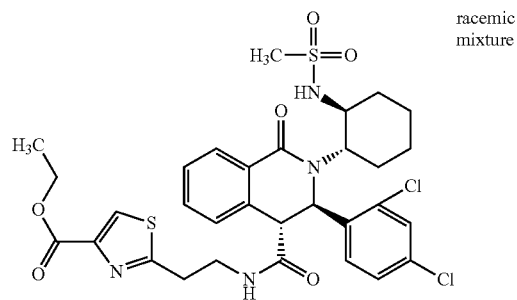


40

45

50

238

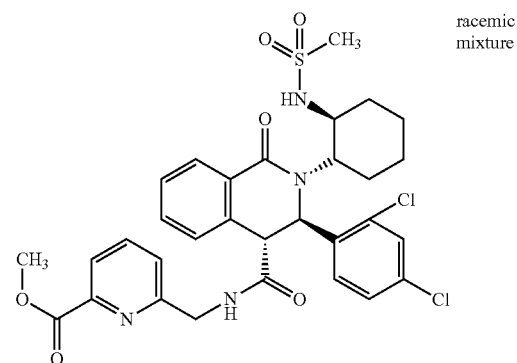


239

55

60

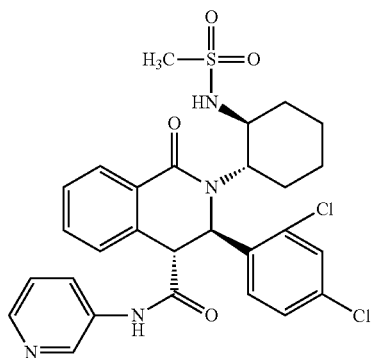
65



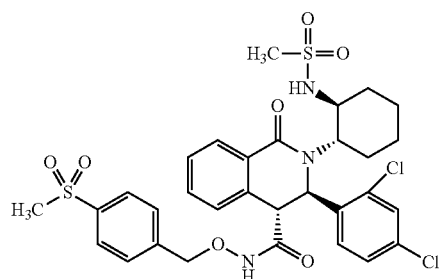
165

TABLE 109

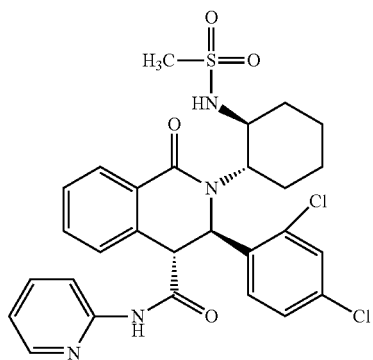
240

racemic
mixture

241

racemic
mixture

242

racemic
mixture

243

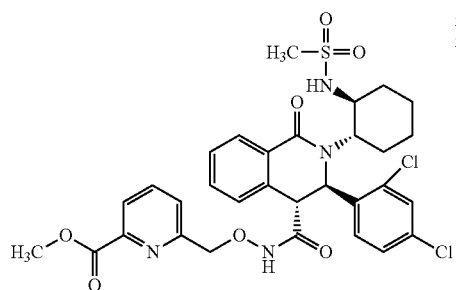
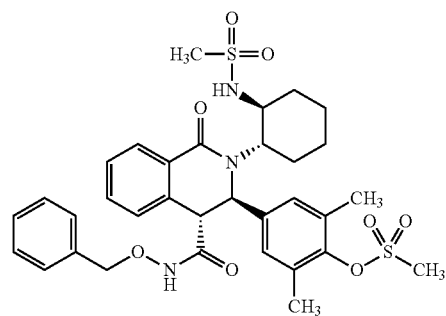
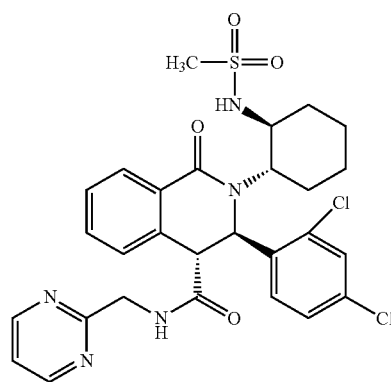
racemic
mixture**166**

TABLE 110

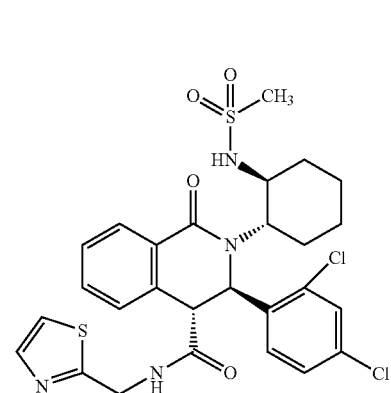
244

racemic
mixture

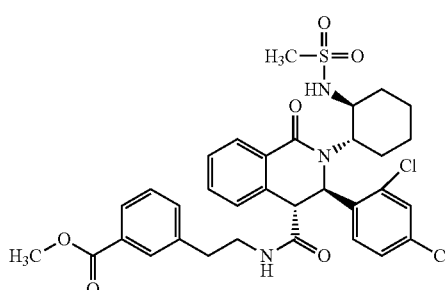
245

racemic
mixture

246

racemic
mixture

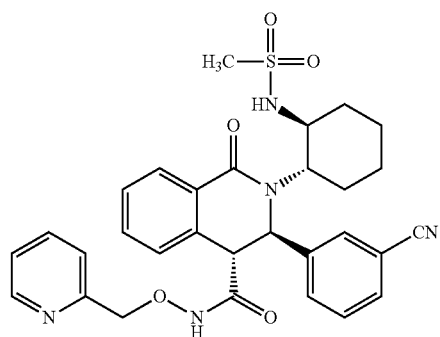
247

racemic
mixture

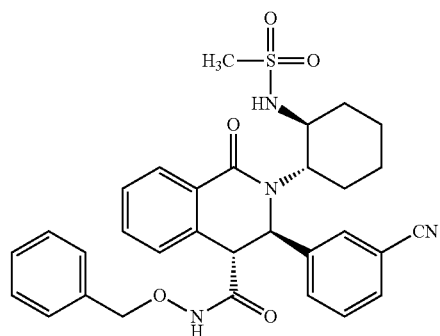
167

TABLE 111

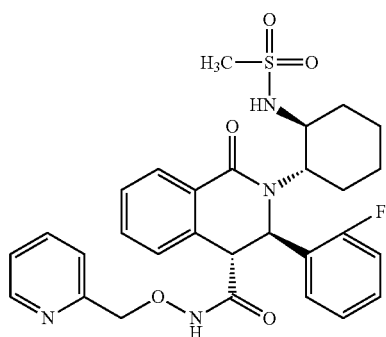
248



249



250



251

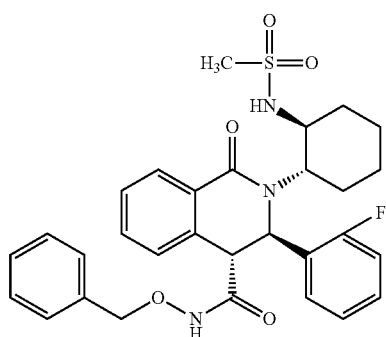
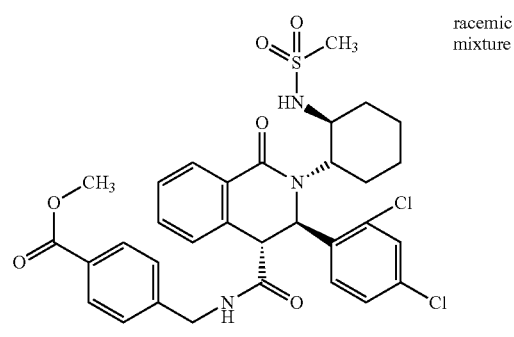
**168**

TABLE 112

252

5

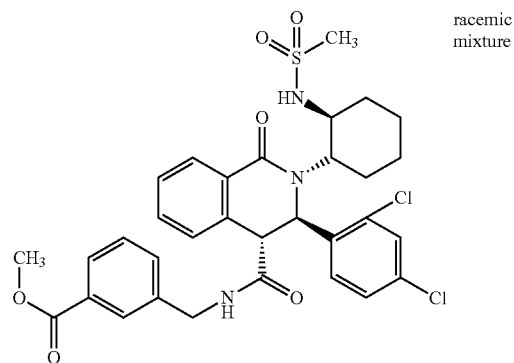


10

15

253

20



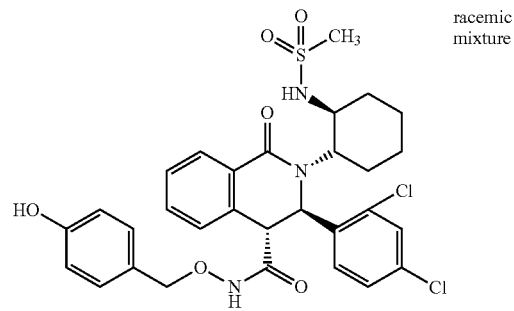
25

30

35

254

40

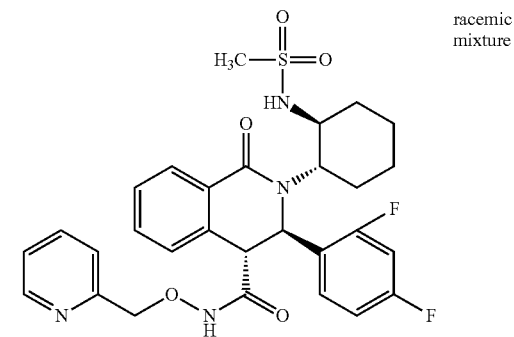


45

50

255

55

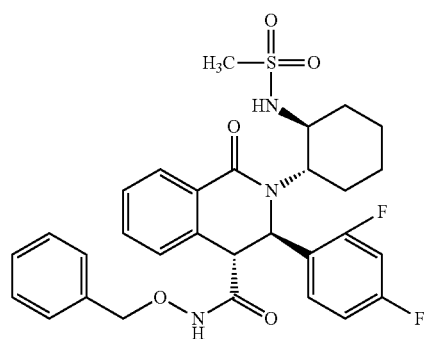


60

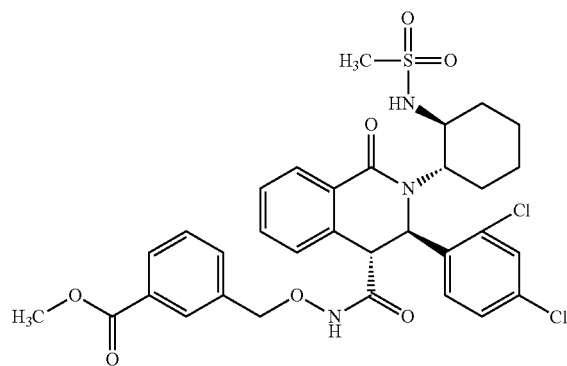
65

TABLE 113

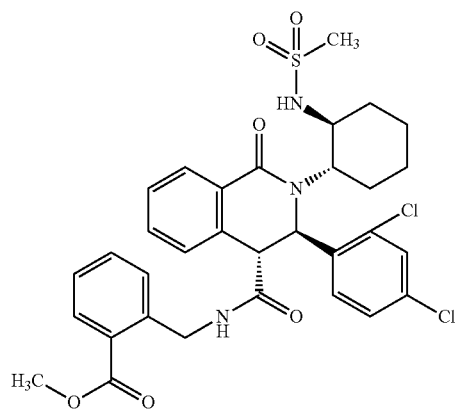
256

racemic
mixture

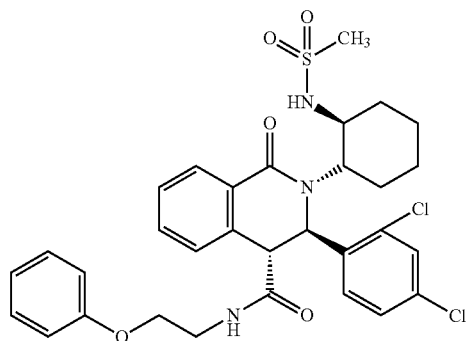
257



258

racemic
mixture

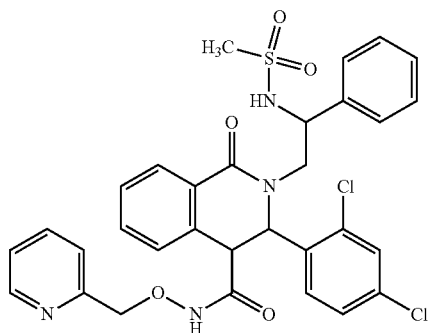
259

racemic
mixture

171

TABLE 114

260



261

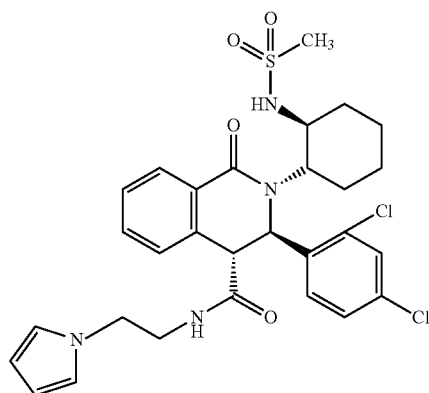
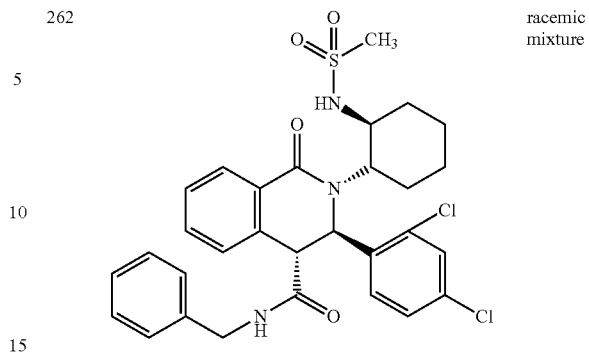
**172**

TABLE 114-continued

262

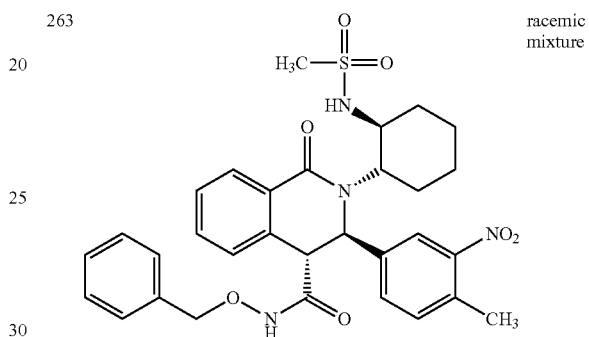


5

10

15

263



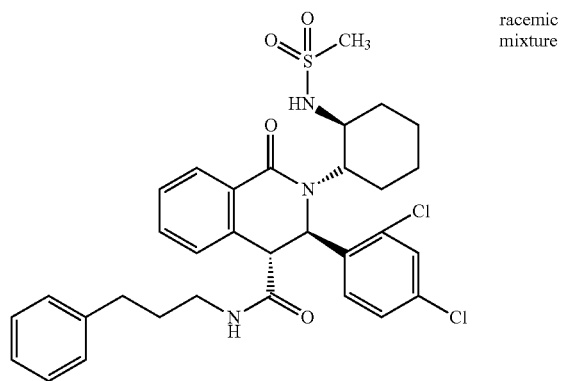
20

25

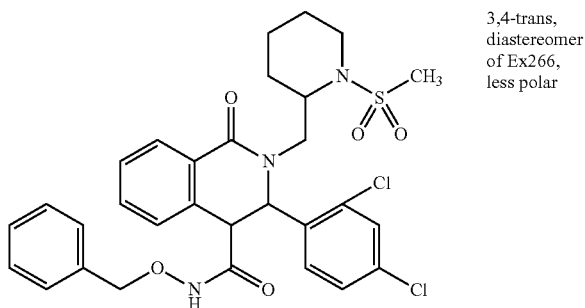
30

TABLE 115

264



265

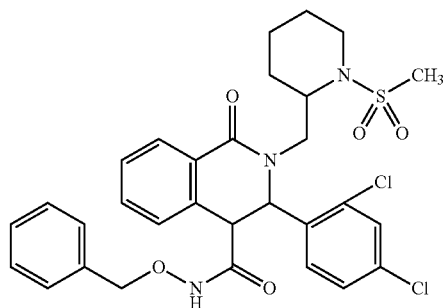


173

174

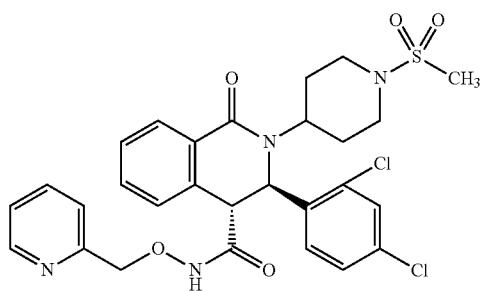
TABLE 115-continued

266



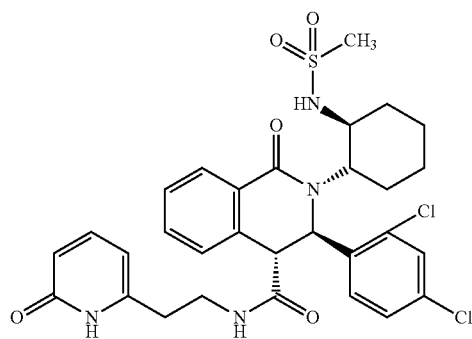
3,4-trans,
diastereomer
of Ex265,
more polar

267



racemic
mixture

268

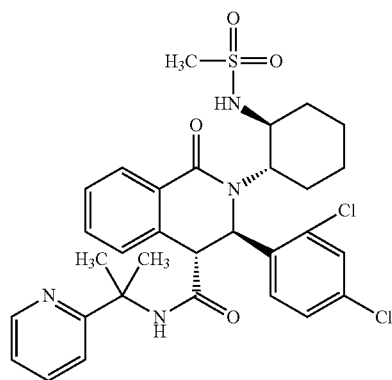


racemic
mixture

TABLE 116

50

269



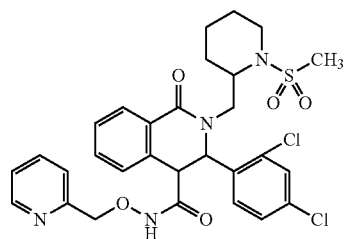
racemic
mixture

TABLE 116-continued

55 270

3,4-trans

60

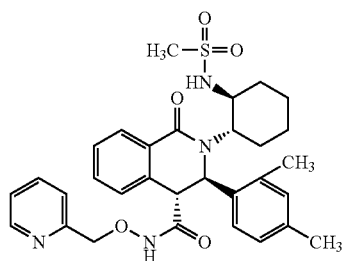


65

175

TABLE 116-continued

271

diastereomer
of Ex275,
more polar

272

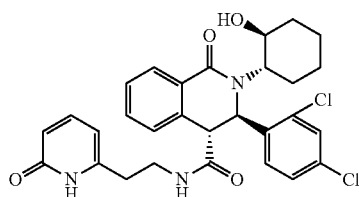
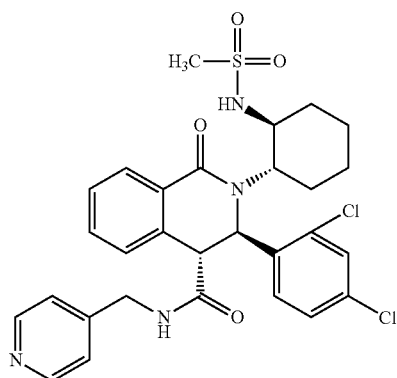
racemic
mixture

TABLE 117

273

racemic
mixture

274

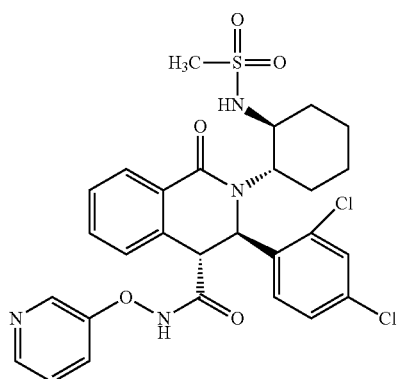
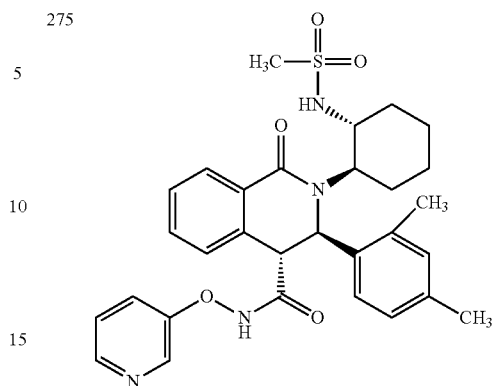
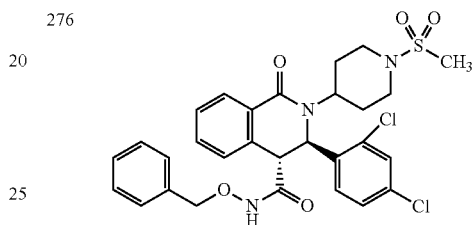
racemic
mixture**176**

TABLE 117-continued

275

diastereomer
of Ex271,
less polar

276

racemic
mixture

277

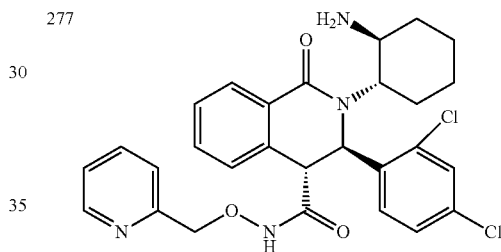
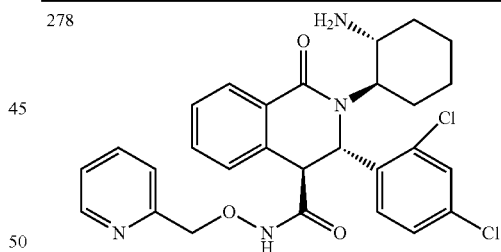


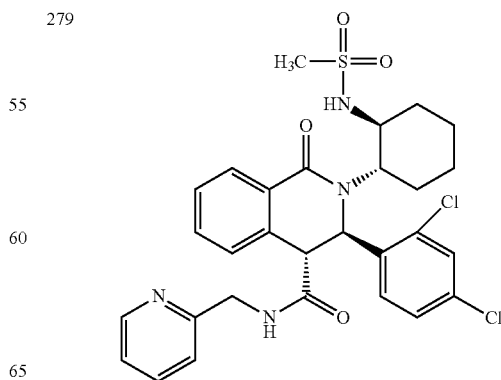
TABLE 118

278



2HCl

279



177

TABLE 118-continued

280

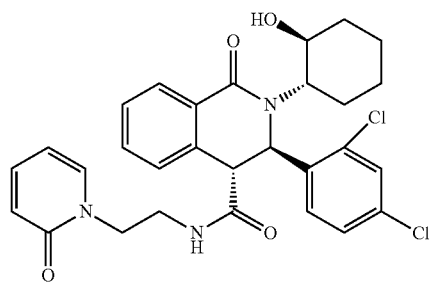
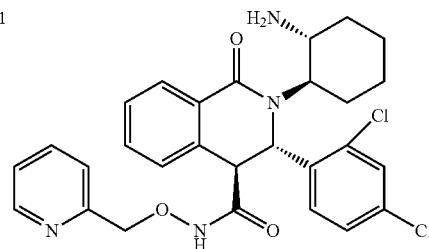
racemic
mixture**178**

TABLE 118-continued

281

5

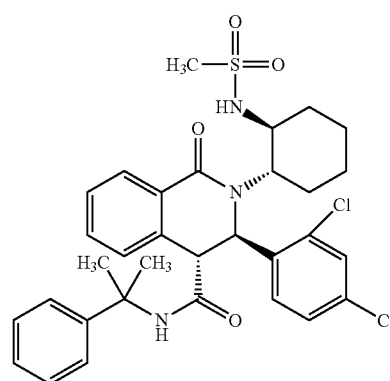
10

racemic
mixture

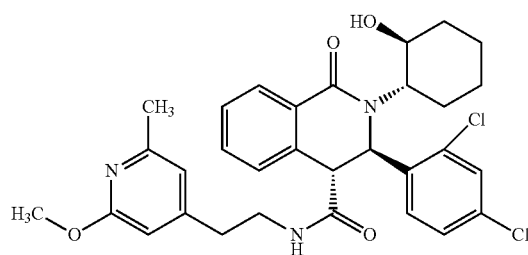
2HCl

TABLE 119

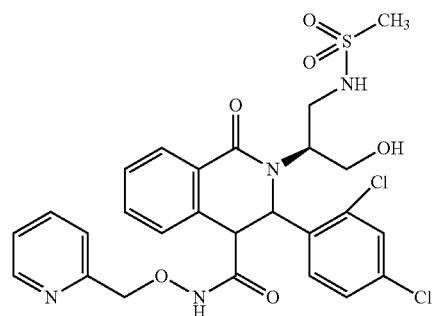
282

racemic
mixture

283

racemic
mixture

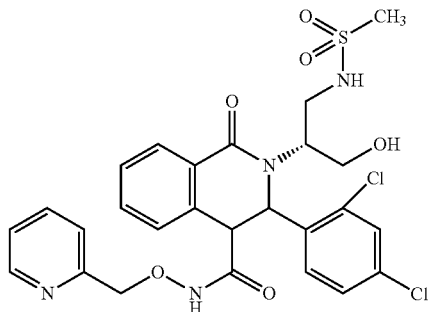
284

3,4-trans,
diastereo
mixture

179

TABLE 119-continued

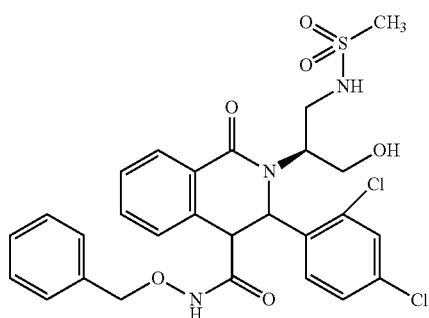
285

3,4-trans,
diastereo
mixture

180

TABLE 120

286

3,4-trans,
diastereo
mixture

287

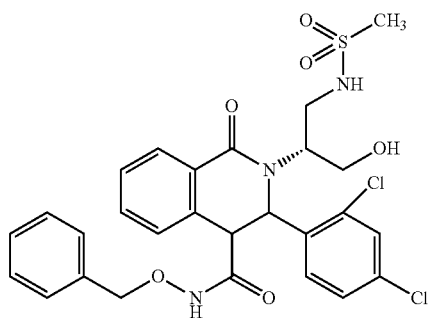
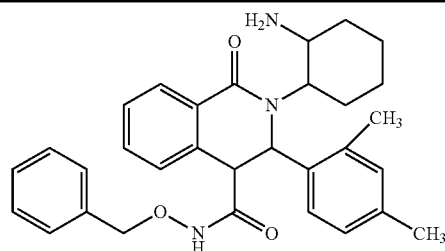
3,4-trans,
diastereo
mixture

TABLE 120-continued

288

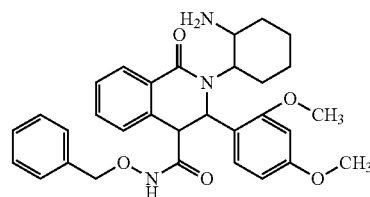
20

1',2'-trans,
3,4-trans,
diastereo
mixture

25

30

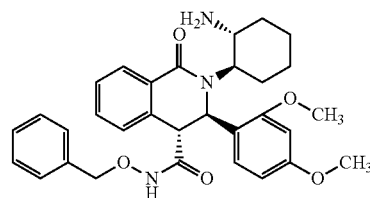
289

1',2'-trans,
3,4-trans,
diastere-
omer
of Ex290,
more polar

35

40

290

racemic
mixture,
diastere-
omer
of Ex289,
less polar

45

TABLE 121

291

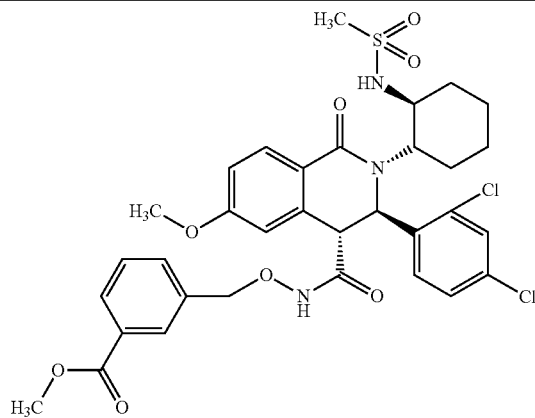
racemic
mixture

TABLE 121-continued

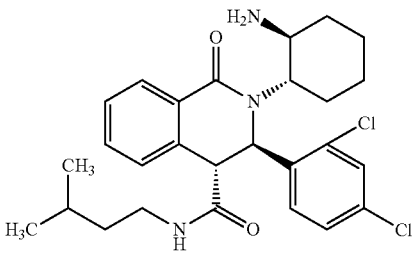
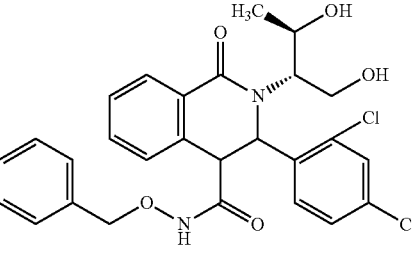
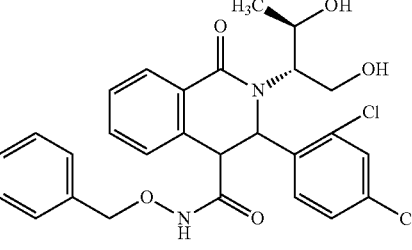
292		racemic mixture
293		3,4-trans, diastereomer of Ex294, less polar
294		3,4-trans, diastereomer of Ex293, more polar

TABLE 122

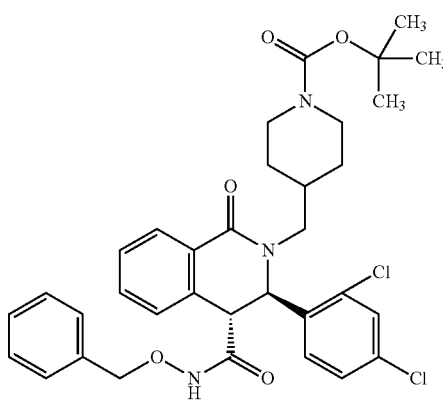
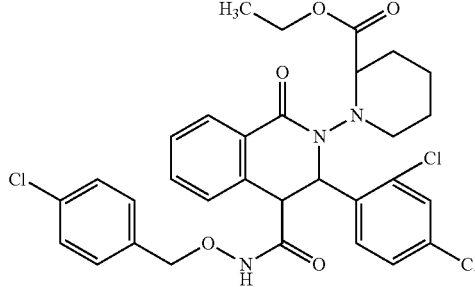
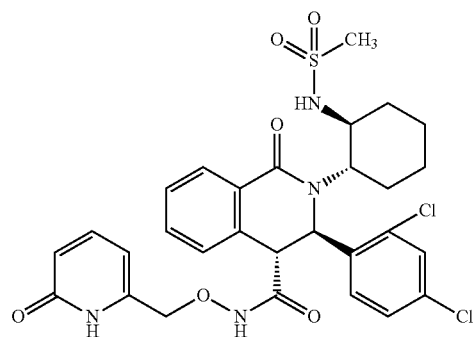
295		racemic mixture
296		3,4-trans

TABLE 122-continued

297

racemic
mixture

298

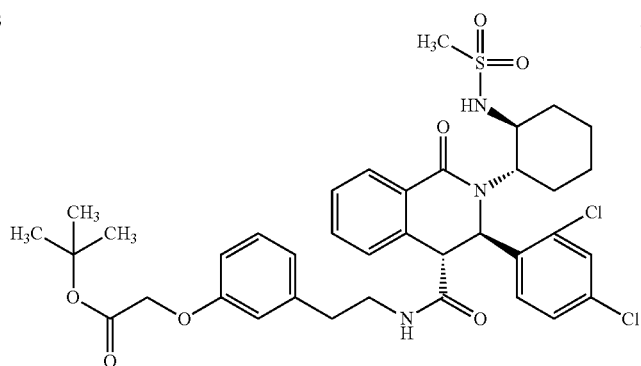
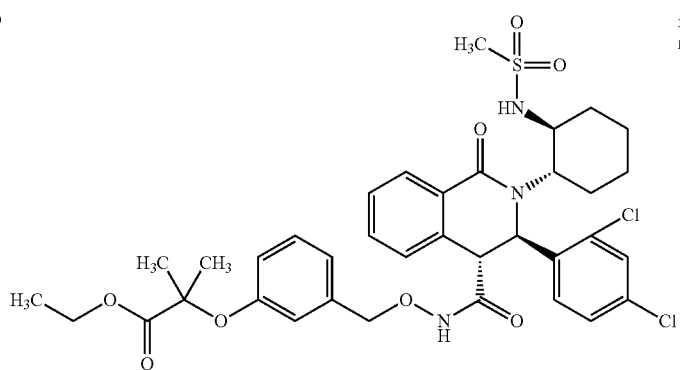
racemic
mixture

TABLE 123

299

racemic
mixture

300

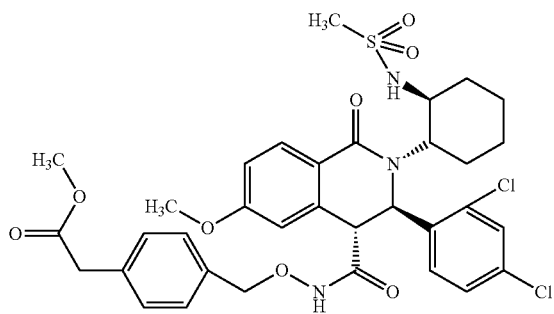
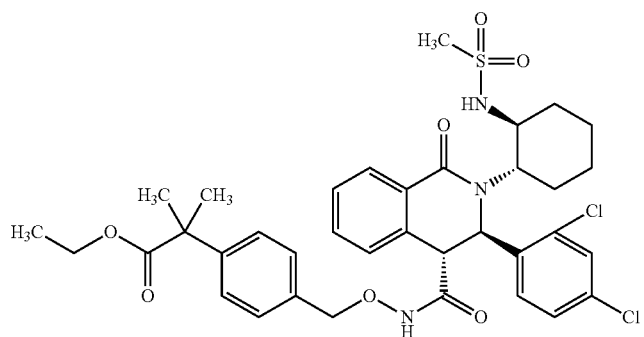
racemic
mixture

TABLE 123-continued

301

racemic
mixture

302

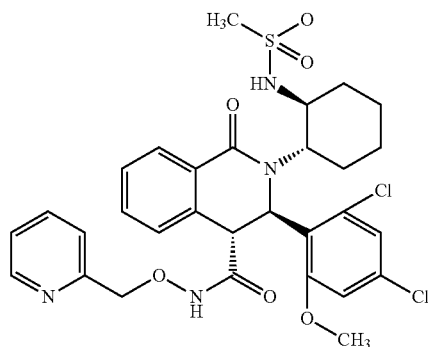
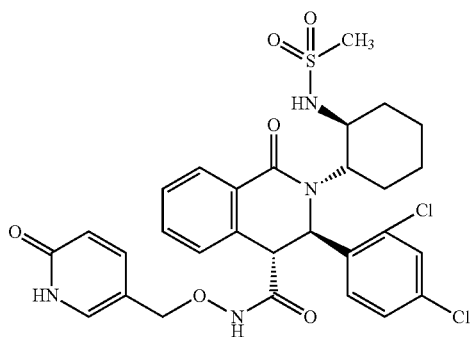
racemic
mixture,
diastereomer
of Ex306,
less polar

TABLE 124

303

racemic
mixture

304

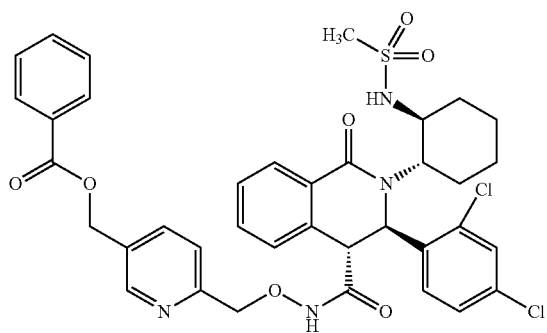
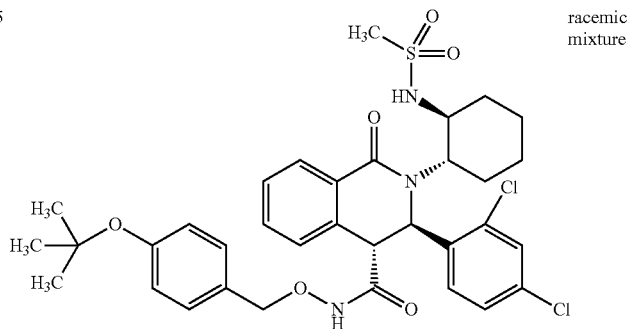
racemic
mixture

TABLE 124-continued

305



306

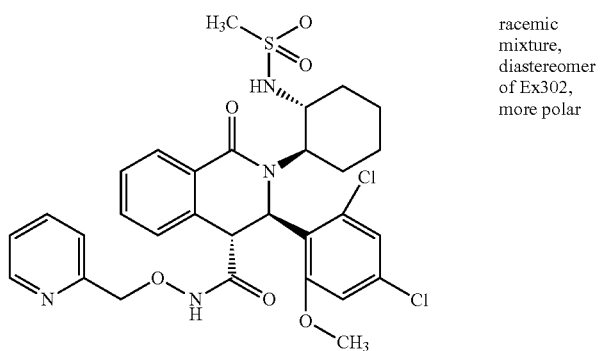
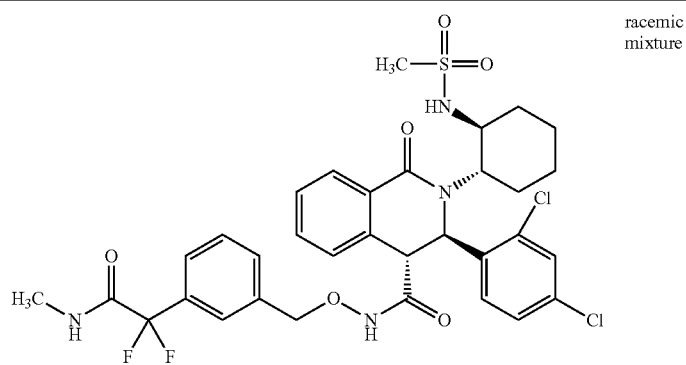


TABLE 125

307



308

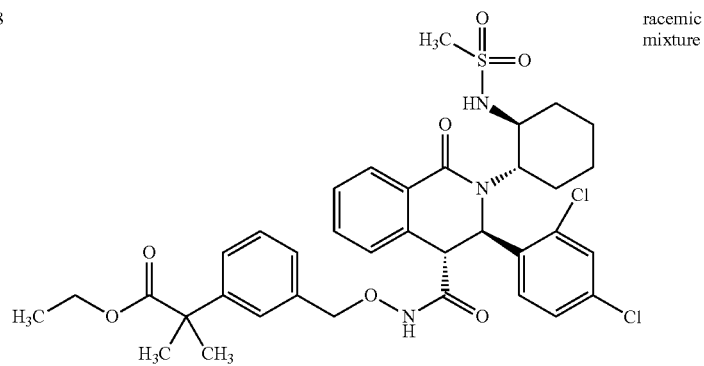


TABLE 125-continued

[illegible]

TABLE 126

311

racemic mixture

Chemical structure 311 is a complex molecule. It features a 1,2,3,4-tetrahydronaphthalene-1-carboxamide core. The core is substituted with a 4-(2-(tert-butoxy)ethoxy)benzyl group at position 1, a 2-chlorophenyl group at position 2, and a 2-chlorophenyl group at position 3. The amide group is attached to a cyclohexyl ring.

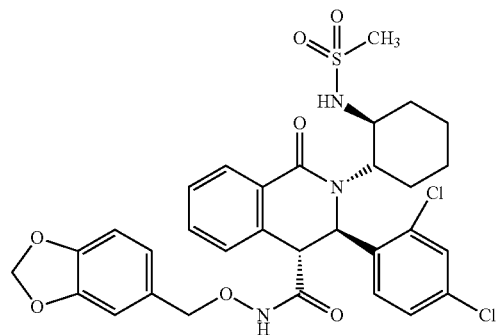
312

racemic mixture

Chemical structure 312 is a complex molecule. It features a 1,2,3,4-tetrahydronaphthalene-1-carboxamide core. The core is substituted with a 4-(2-(tert-butoxy)ethoxy)benzyl group at position 1, a 2-chlorophenyl group at position 2, and a 2-chlorophenyl group at position 3. The amide group is attached to a cyclohexyl ring.

TABLE 126-continued

313

racemic
mixture

314

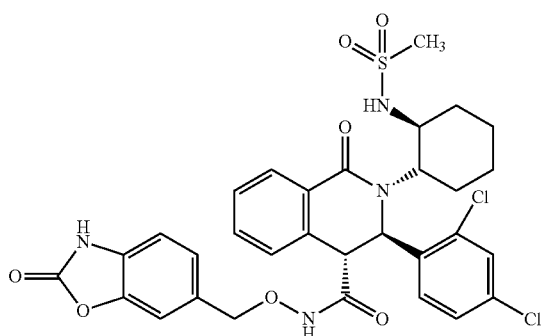
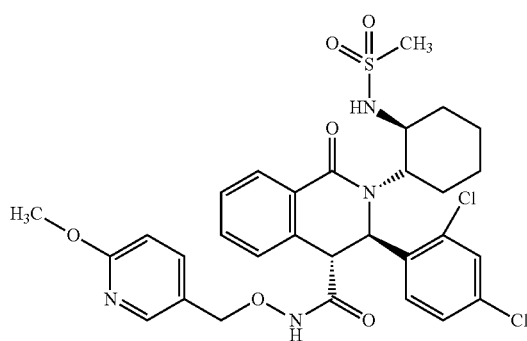
racemic
mixture

TABLE 127

315

racemic
mixture

316

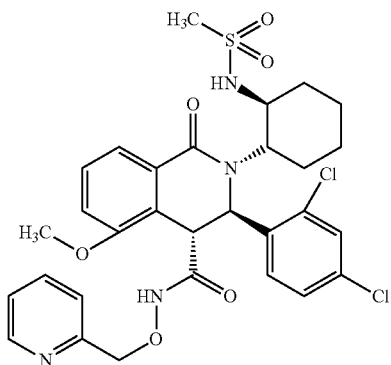
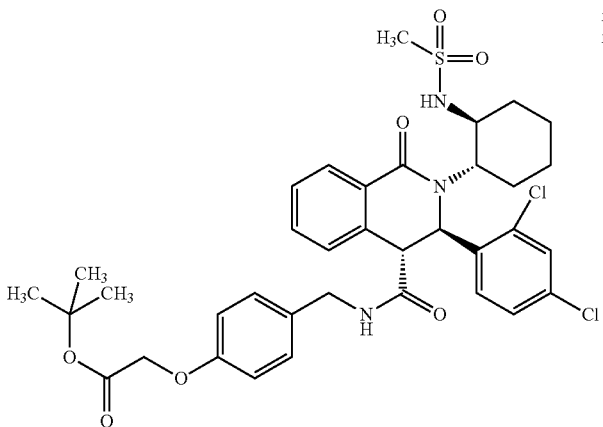
racemic
mixture

TABLE 127-continued

317

racemic
mixture

318

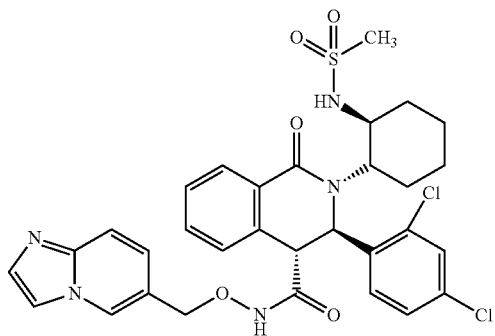
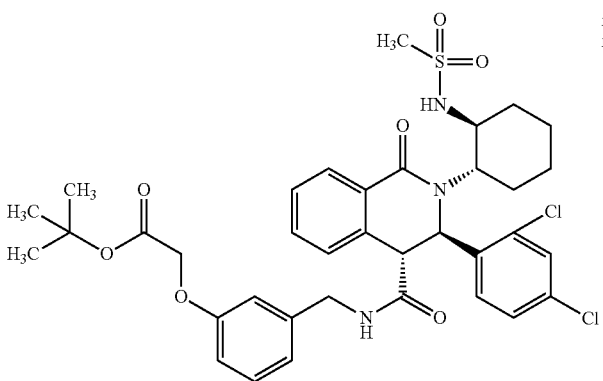
racemic
mixture

TABLE 128

319

racemic
mixture

320

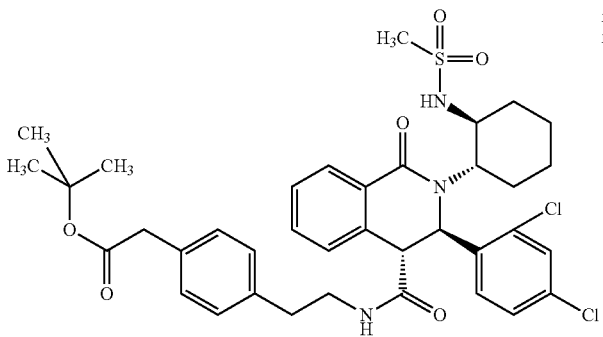
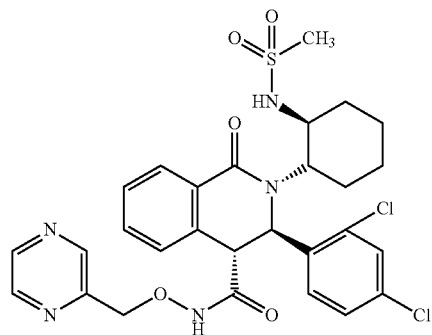
racemic
mixture

TABLE 128-continued

321

racemic
mixture

322

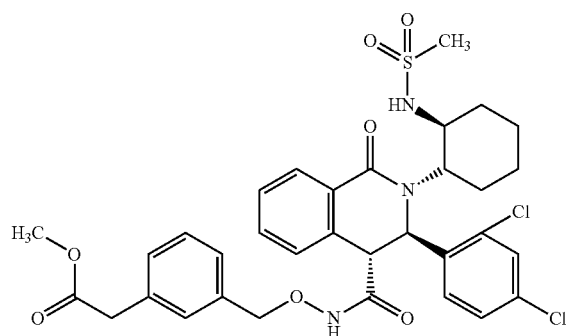
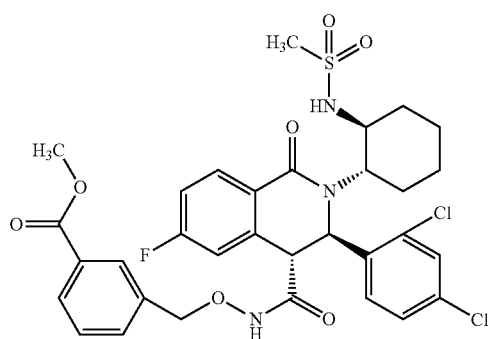
racemic
mixture

TABLE 129

323

racemic
mixture

324

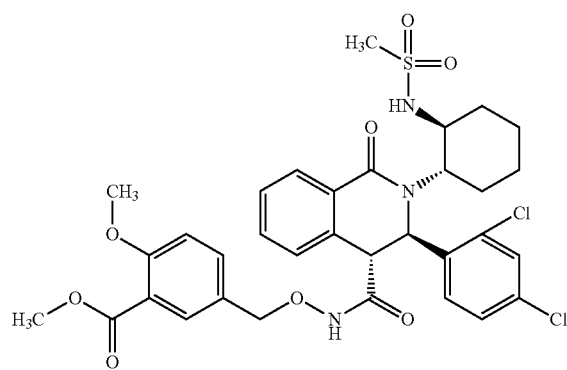
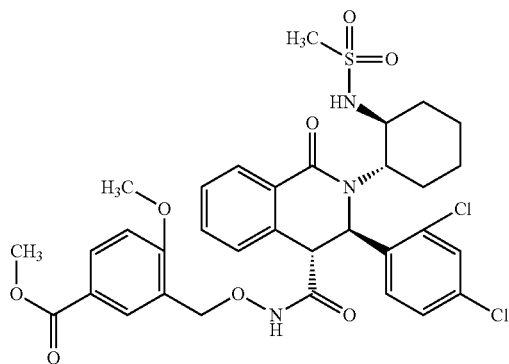
racemic
mixture

TABLE 129-continued

325

racemic
mixture

326

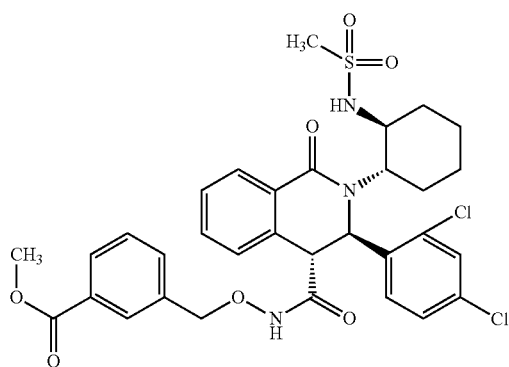
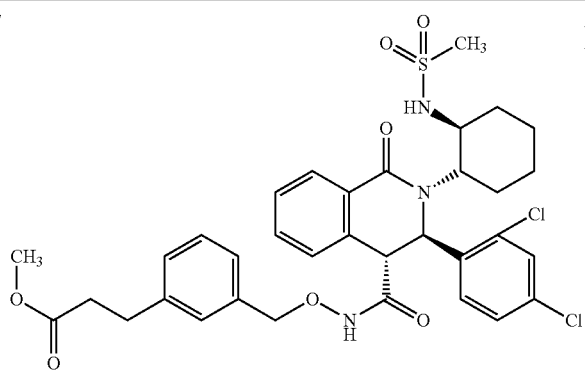
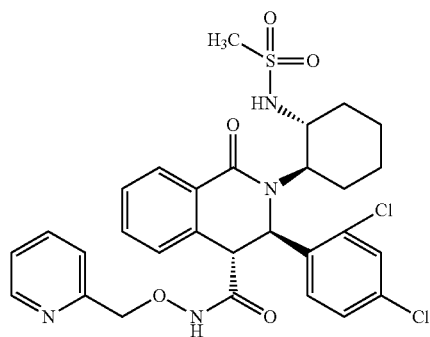
racemic
mixture

TABLE 130

327

racemic
mixture

328

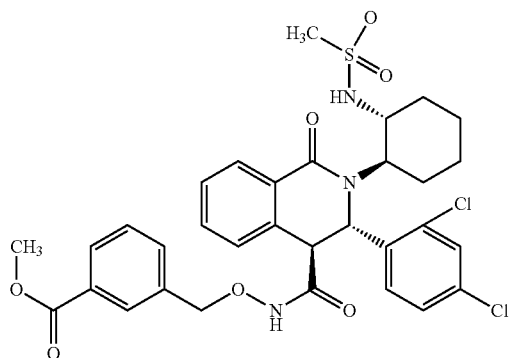


199

200

TABLE 130-continued

329



330

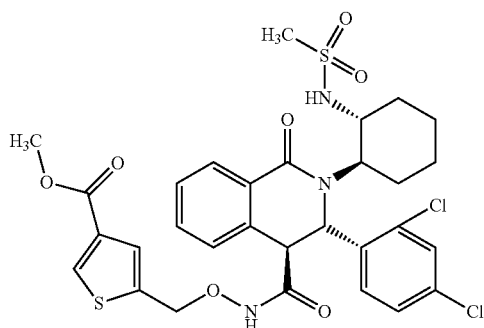
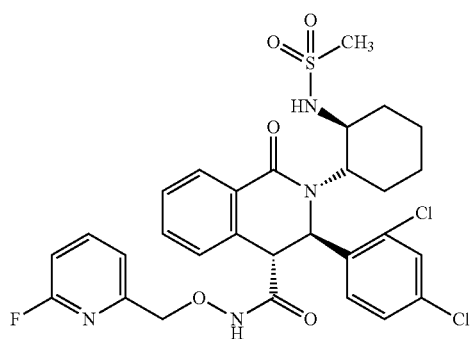


TABLE 131

331

racemic
mixture

332

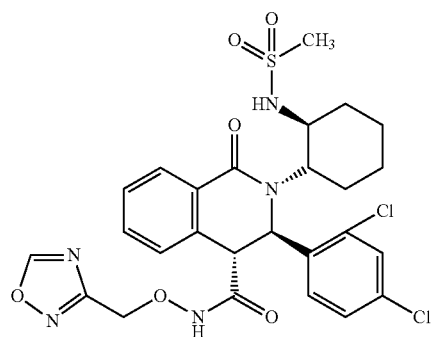
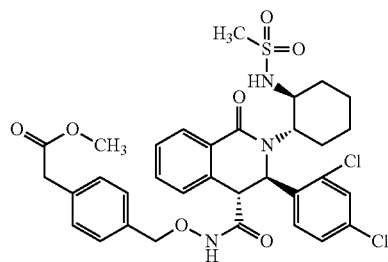


TABLE 131-continued

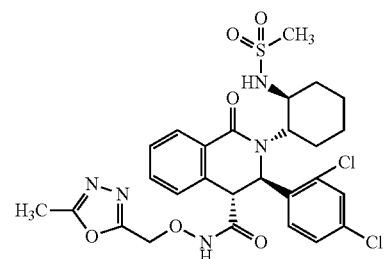
333



50

55

334

racemic
mixture

65

201

TABLE 132

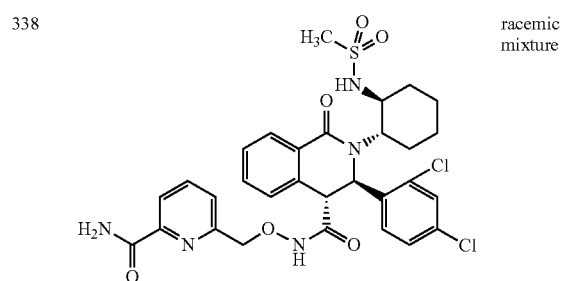
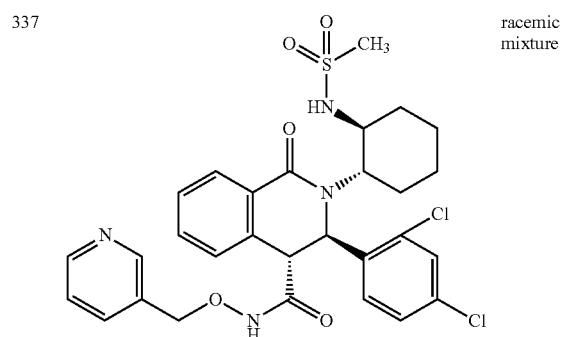
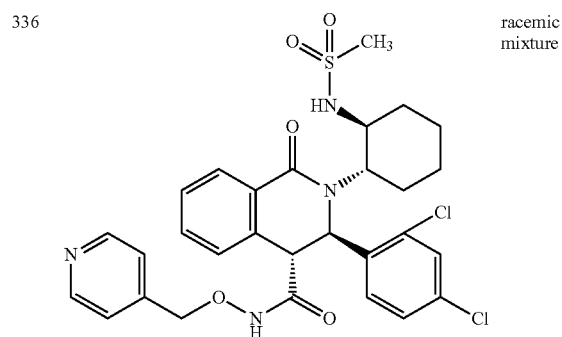
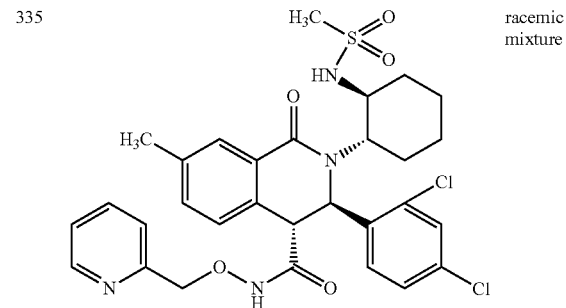
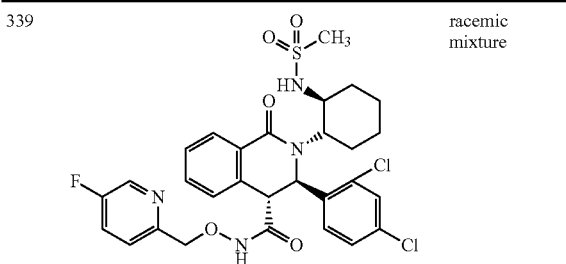


TABLE 133



202

TABLE 133-continued

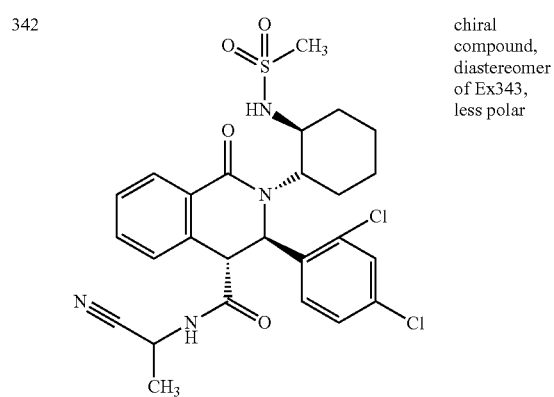
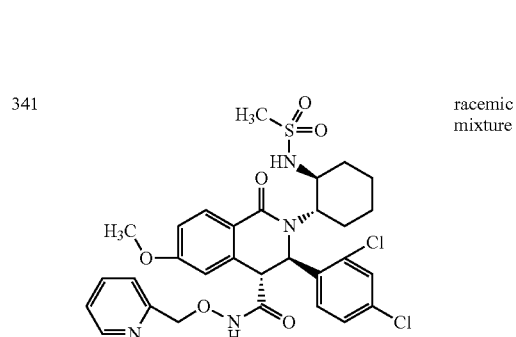
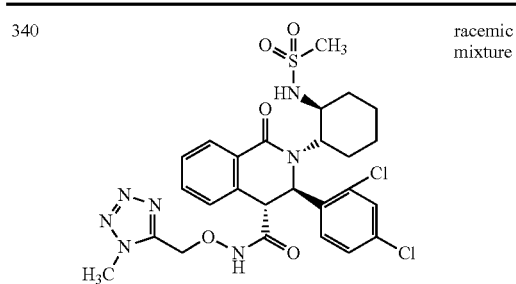
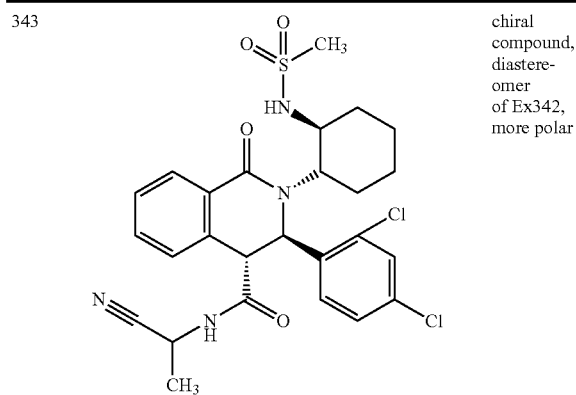


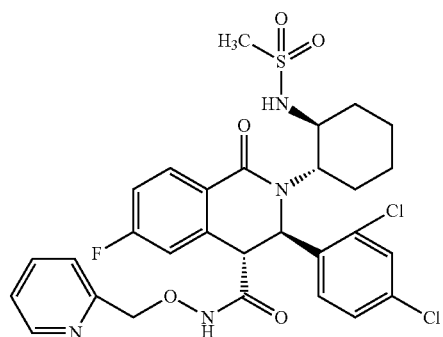
TABLE 134



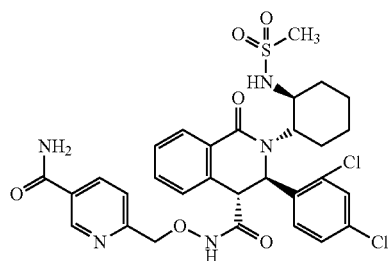
203

TABLE 134-continued

344



345



346

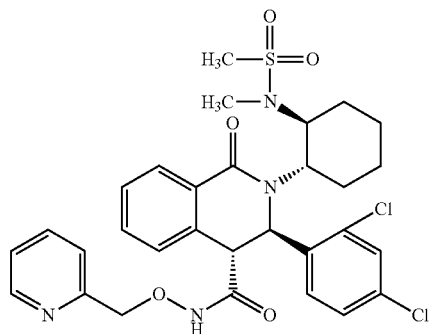
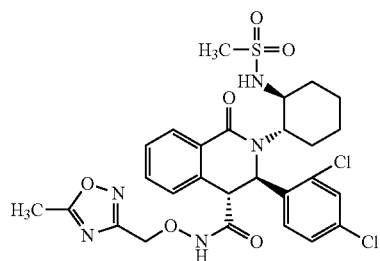
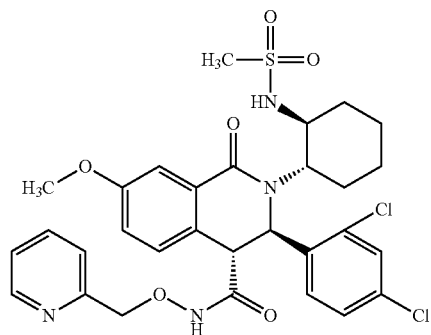


TABLE 135

347



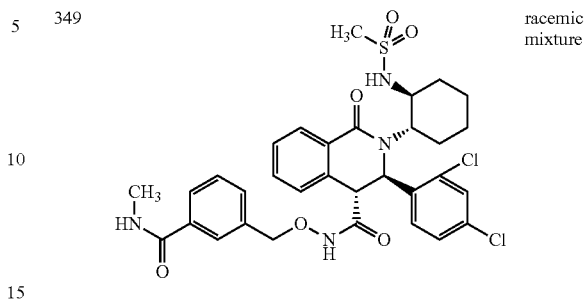
348



204

TABLE 135-continued

5 349



20 350

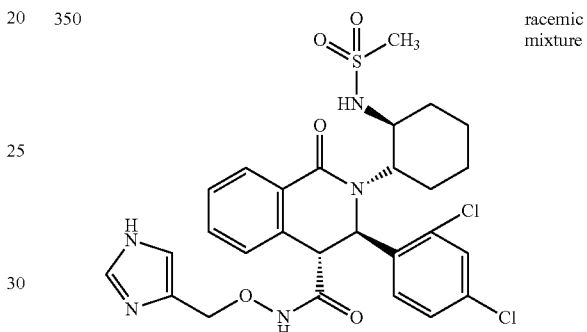
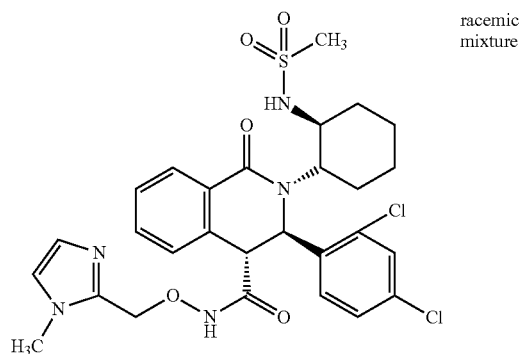
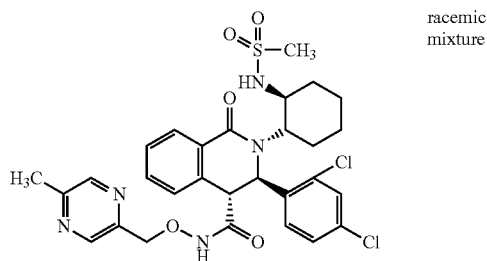


TABLE 136

351



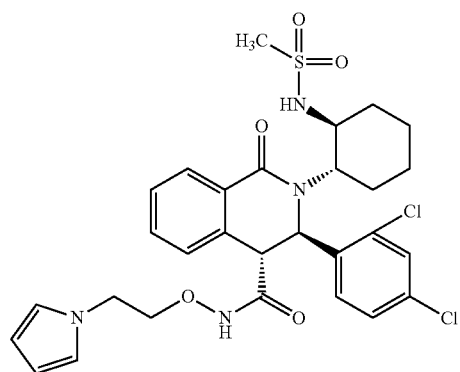
352



205

TABLE 136-continued

353



354

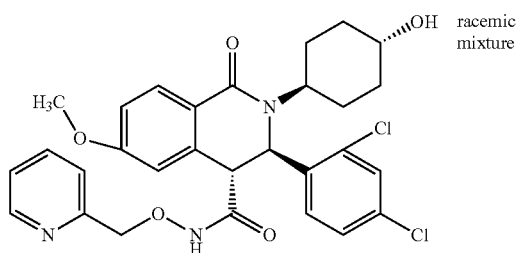
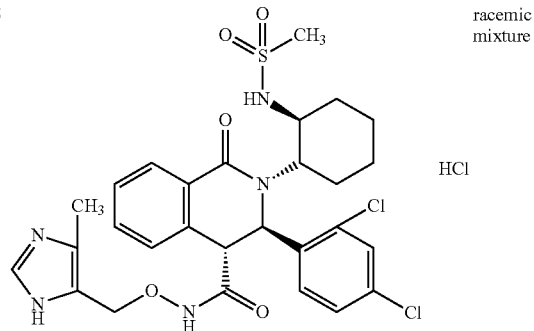
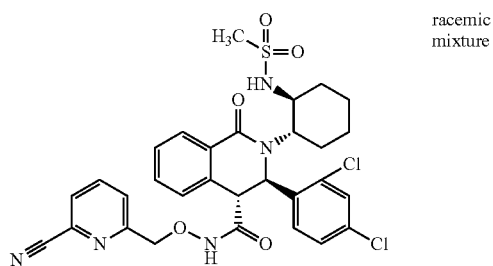


TABLE 137

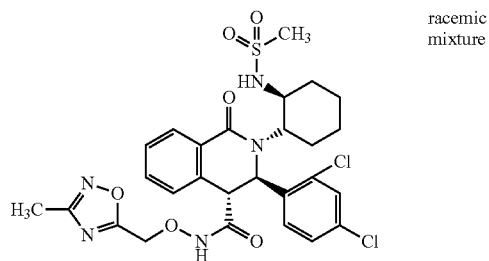
355



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206

TABLE 137-continued

358

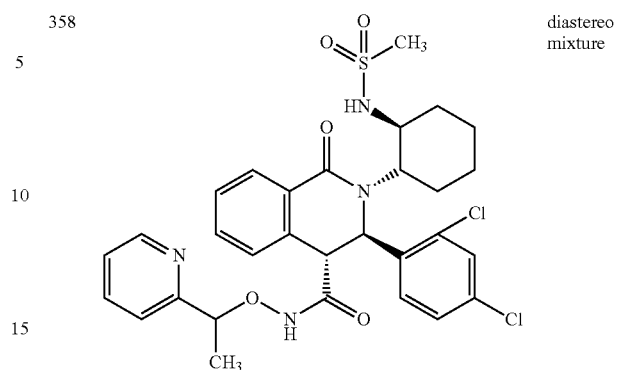
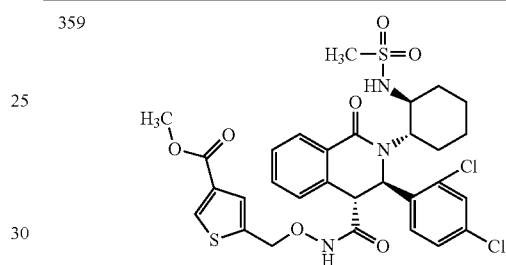
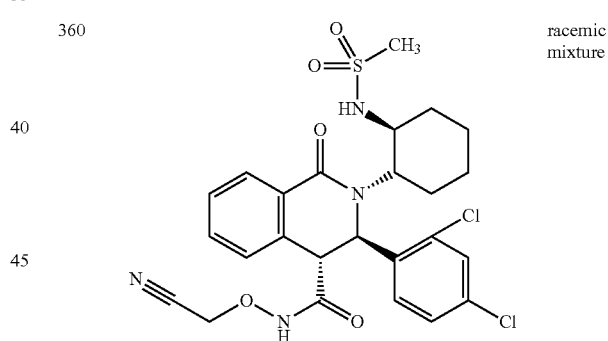


TABLE 138

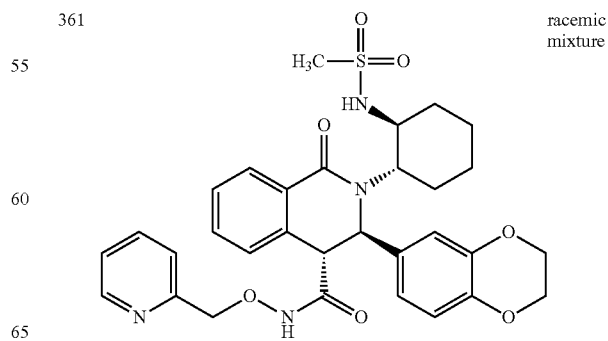
359



360

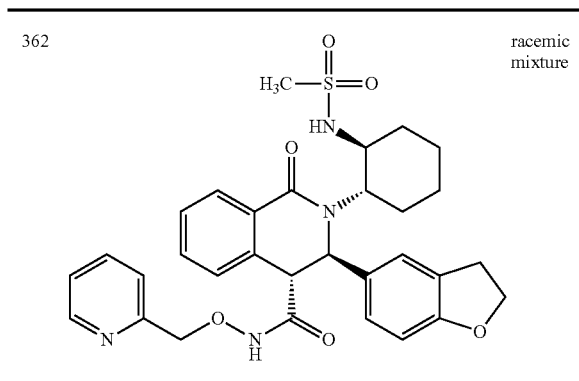


361



207

TABLE 138-continued



208

TABLE 139-continued

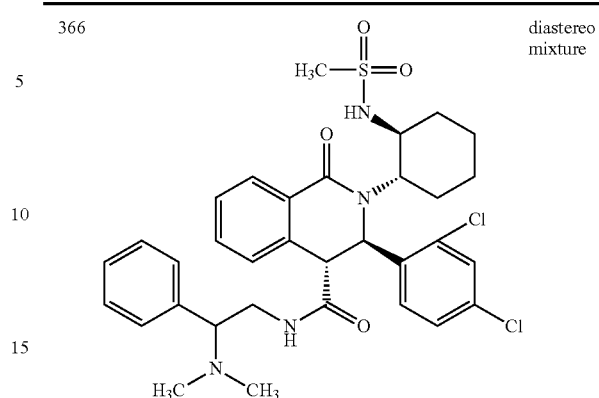


TABLE 139

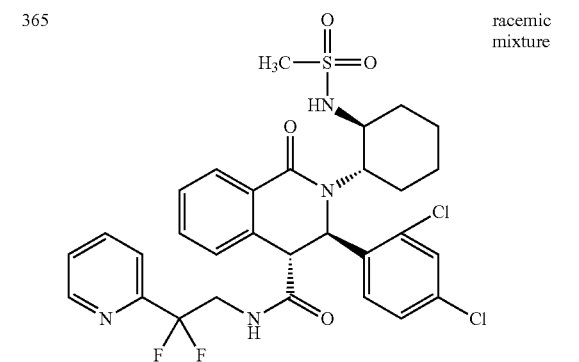
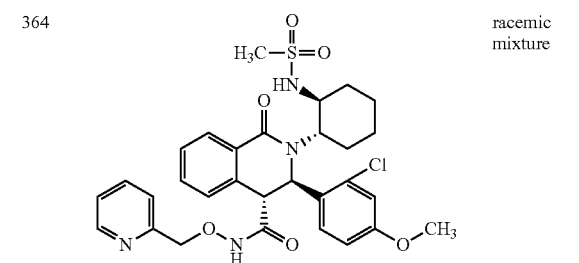
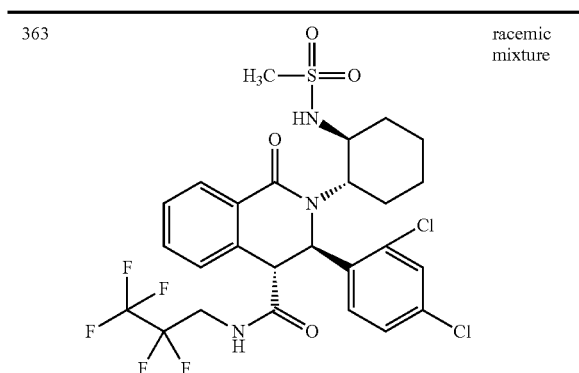
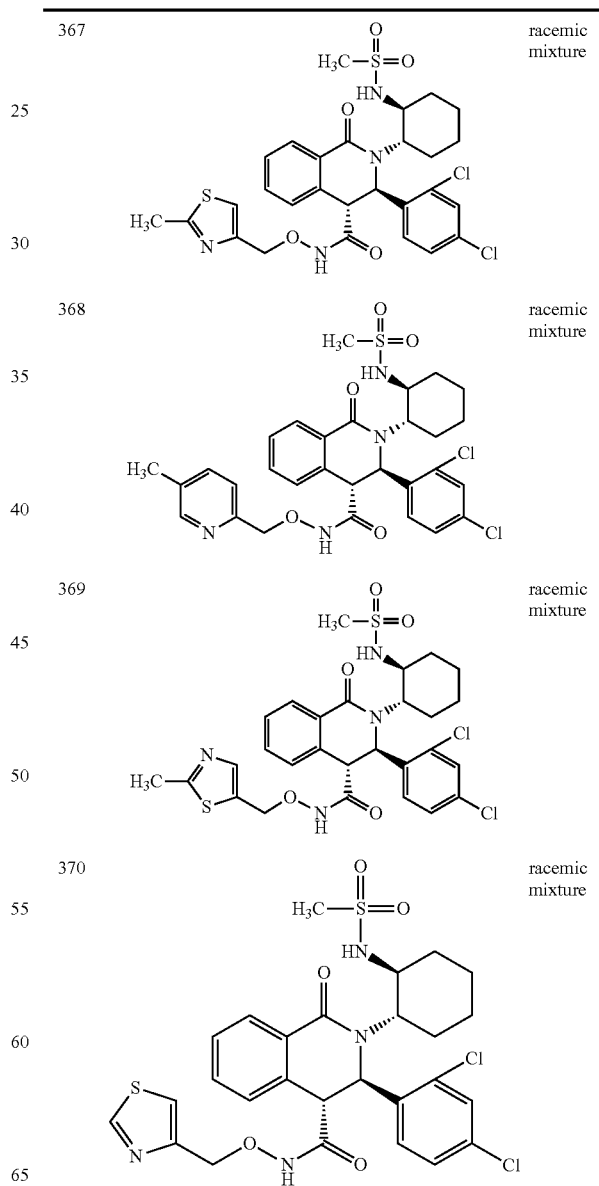


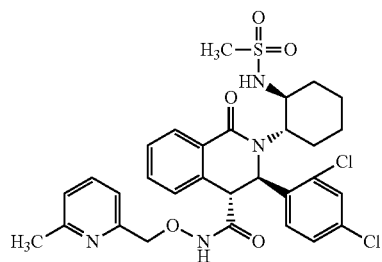
TABLE 140



209

TABLE 141

371

racemic
mixture

372

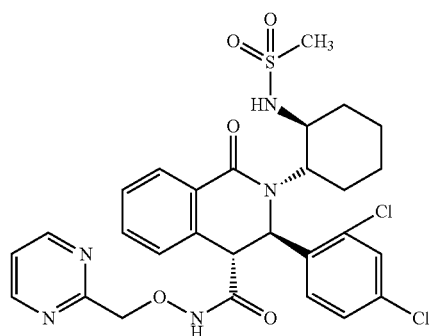
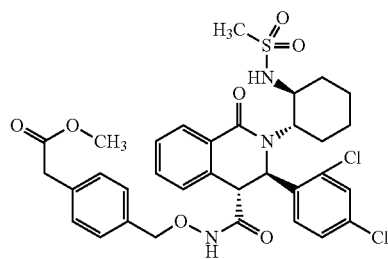
racemic
mixture**210**

TABLE 141-continued

373
5racemic
mixture

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980

985

990

995

1000

1005

1010

1015

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1080

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1100

1105

1110

1115

1120

1125

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1140

1145

1150

1155

1160

1165

1170

1175

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1185

1190

1195

1200

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1660

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1685

1690

1695

1700

1705

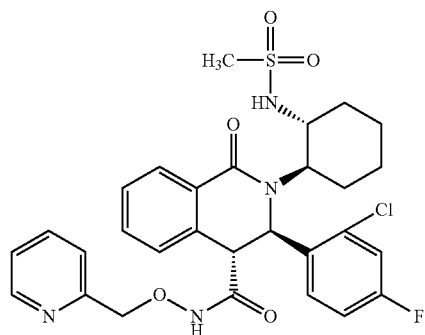
1710

17

211

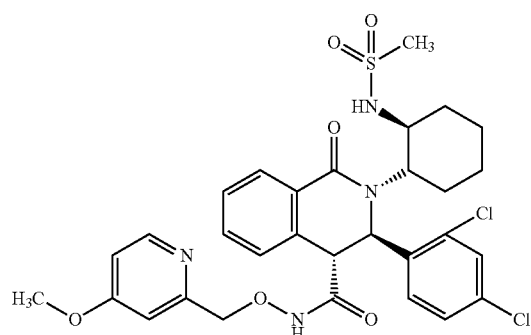
TABLE 142-continued

377



racemic
mixture,
diastereomer
of Ex375,
less polar

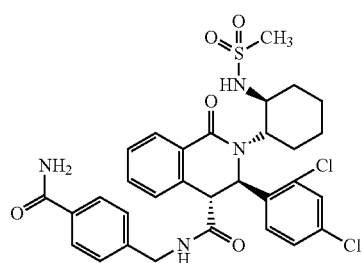
378



racemic
mixture

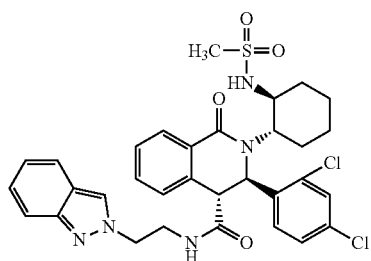
TABLE 143

379



racemic
mixture

380

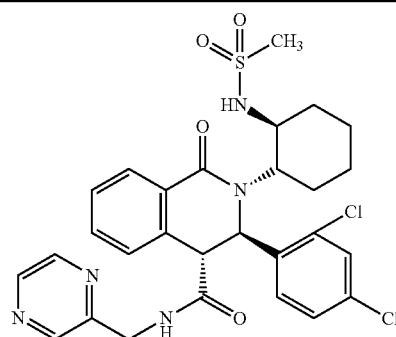


racemic
mixture

TABLE 143-continued

381

40



racemic
mixture

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382

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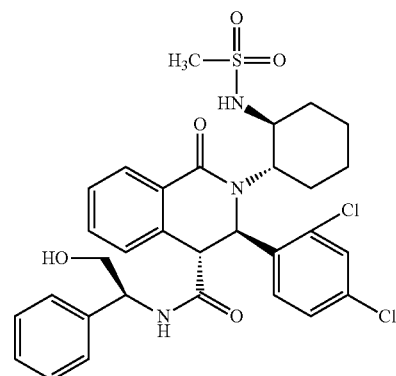
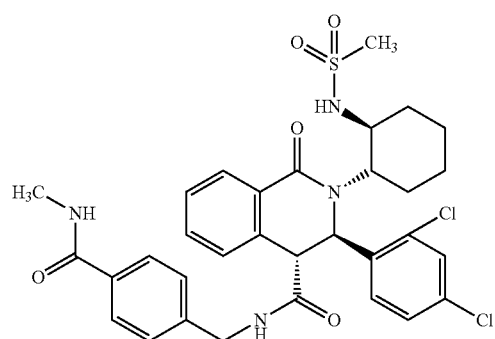
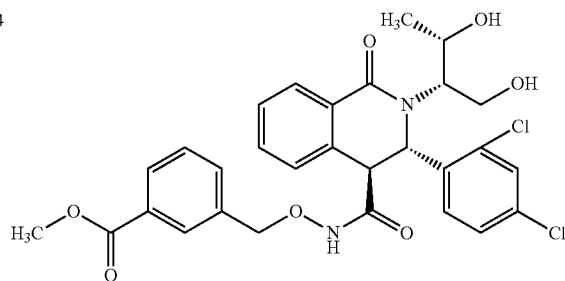


TABLE 144

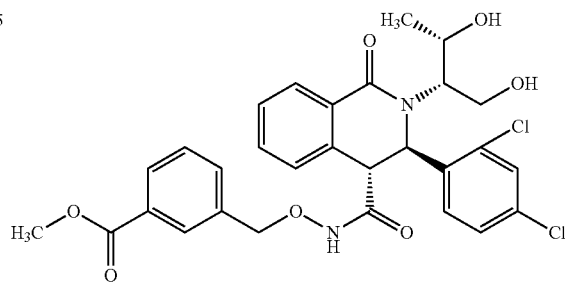
383

racemic
mixture

384



385



386

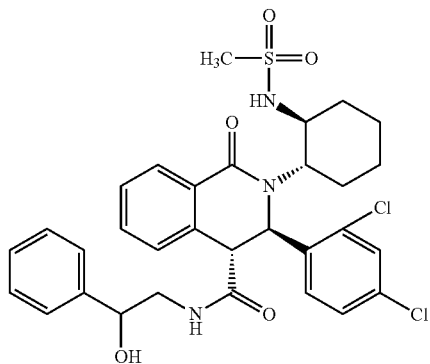
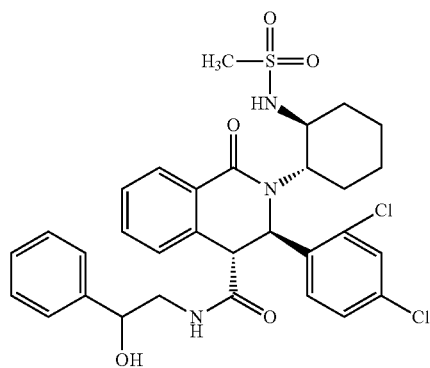
chiral
compound,
diastereomer
of Ex387,
less polar

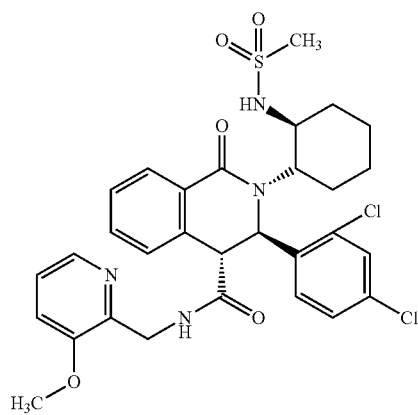
TABLE 145

387



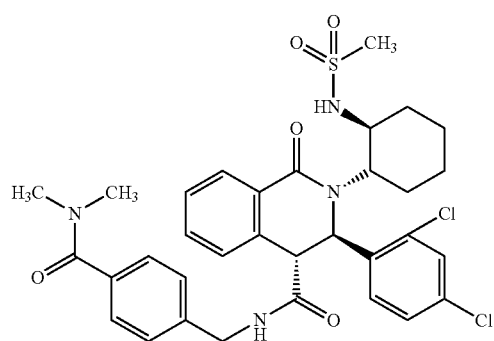
chiral
compound,
diastereomer
of Ex386,
more polar

388



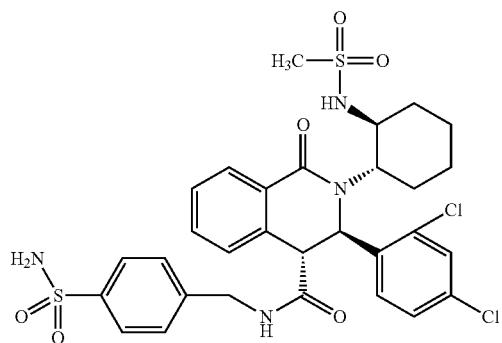
racemic
mixture

389



racemic
mixture

390

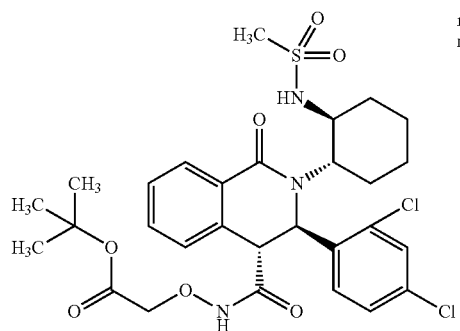


racemic
mixture

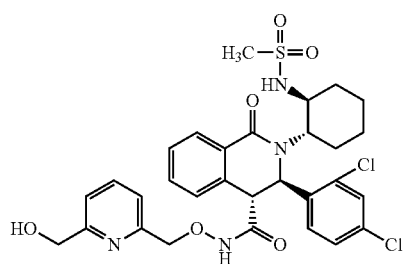
217

TABLE 146

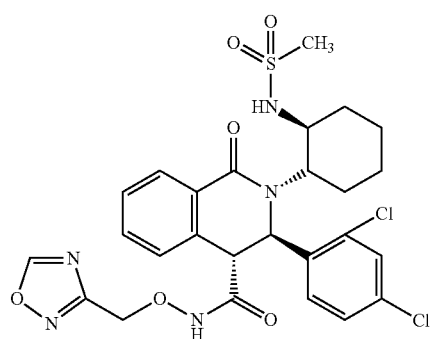
391

racemic
mixture

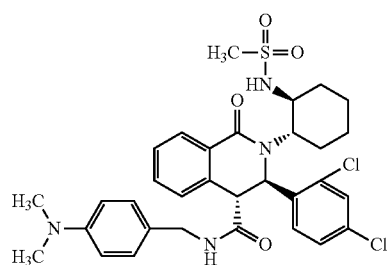
392

racemic
mixture

393

racemic
mixture

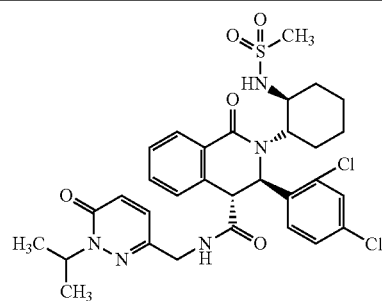
394

racemic
mixture

218

TABLE 147

395

racemic
mixture

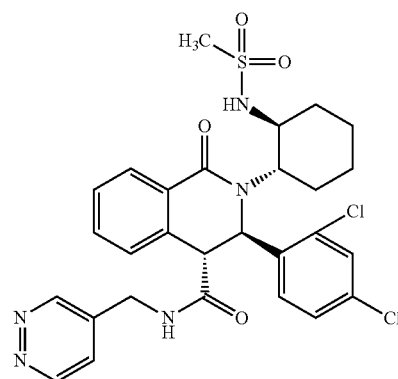
5

10

15

20

396

racemic
mixture

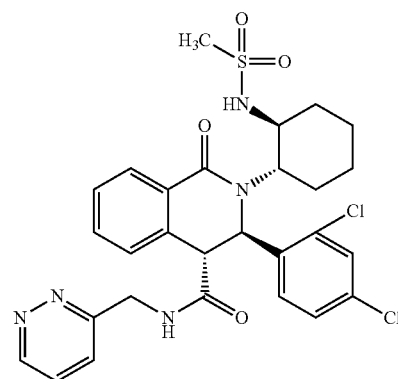
25

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397

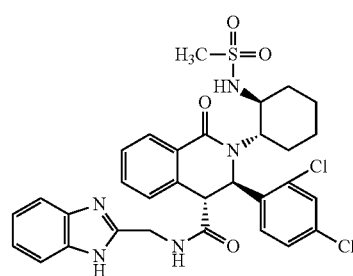
racemic
mixture

45

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398

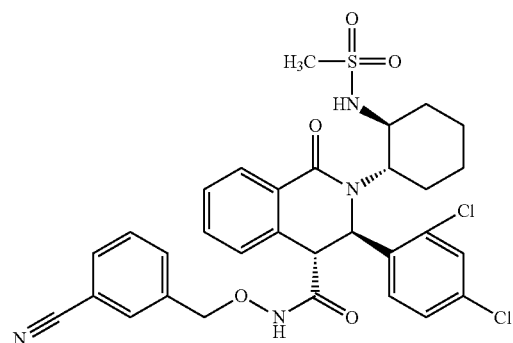
racemic
mixture

60

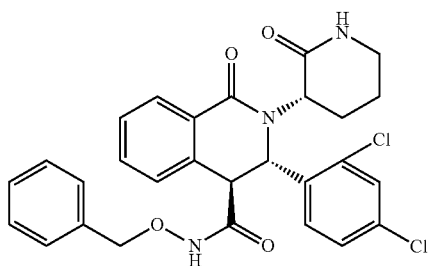
65

TABLE 148

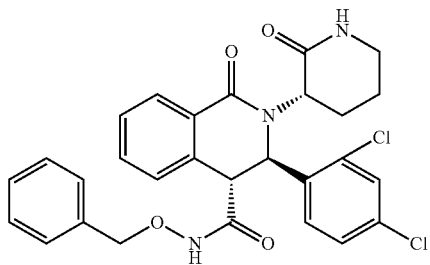
399

racemic
mixture

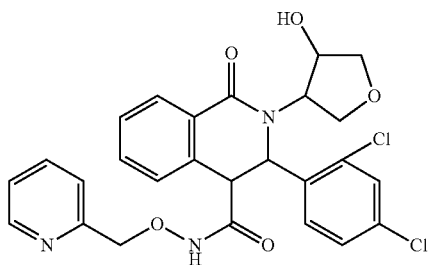
400



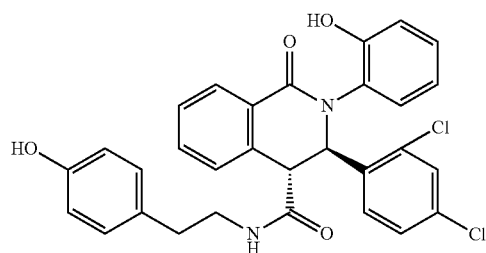
401



402

1',2'-trans,
3,4-trans,
diastereomer
of Ex404

403

racemic
mixture

221

TABLE 149

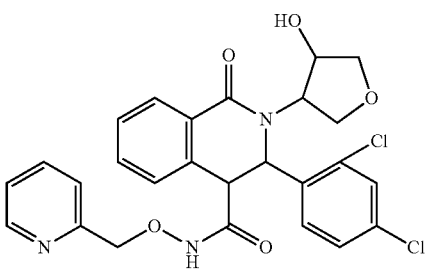
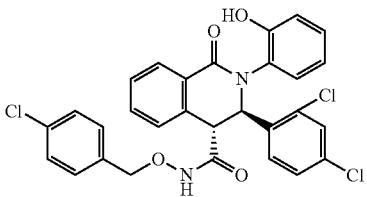
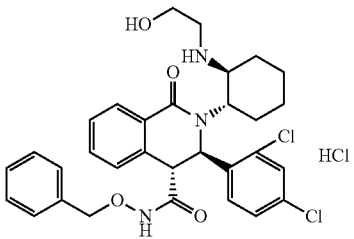
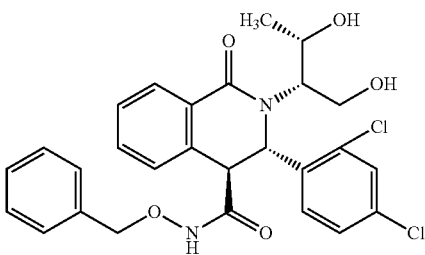
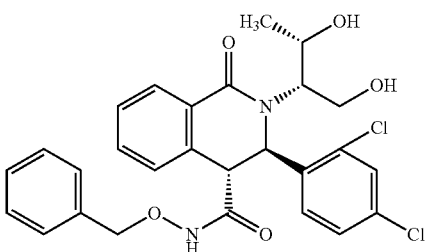
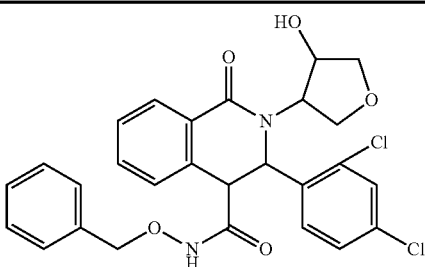
404		1',2' -trans, 3,4-trans, diastereomer of Ex402
405		racemic mixture
406		racemic mixture
407		
408		

TABLE 150

409		1',2' -trans, 3,4-trans, diastereomer of Ex203
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222

TABLE 150-continued

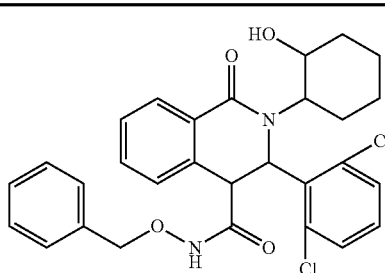
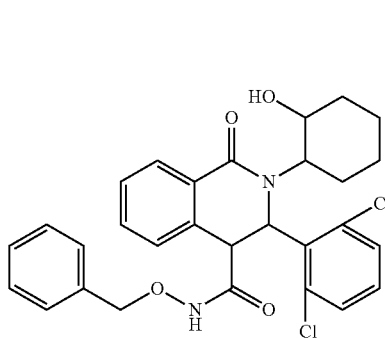
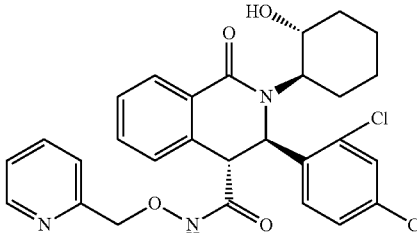
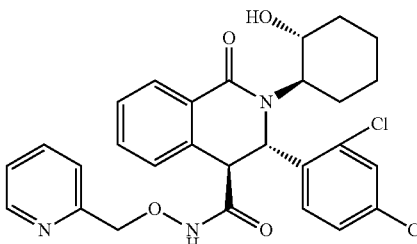
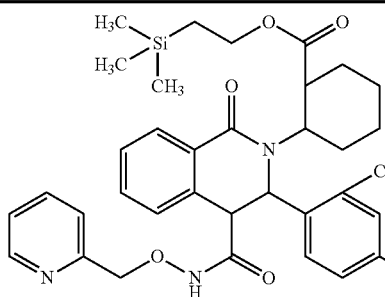
410		1',2' -trans, 3,4-trans, diastereomer of Ex411 less polar
411		1',2' -trans, 3,4-trans, diastereomer of Ex410 more polar
412		racemic mixture, 1',2' -cis, 3,4-trans, diastereomer of Ex28
413		

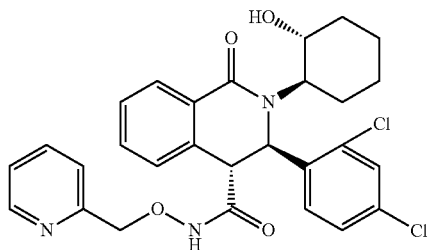
TABLE 151

414		1',2' -trans, 3,4-trans
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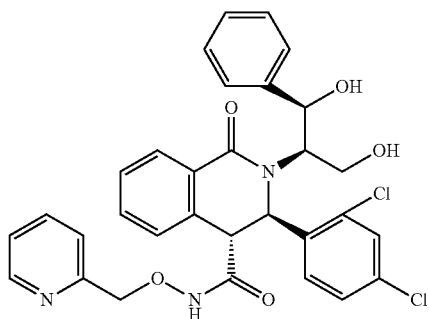
223

TABLE 151-continued

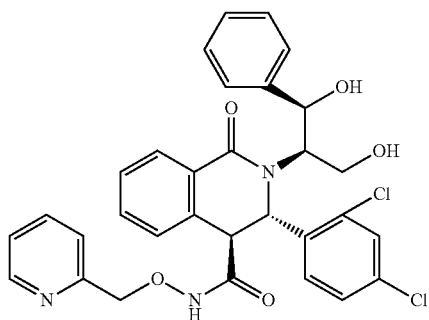
415



416



417



418

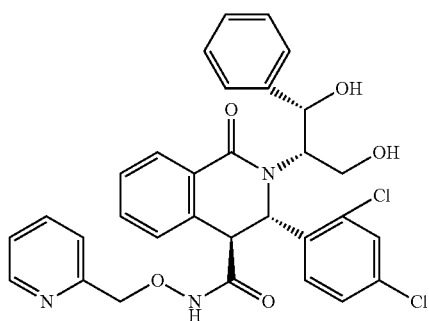


TABLE 152

419

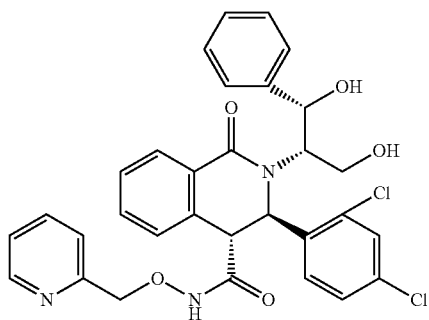
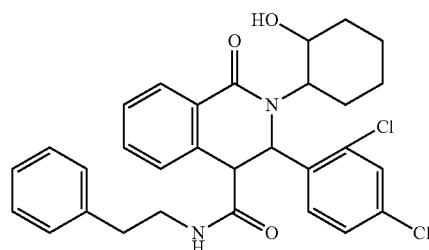
**224**

TABLE 152-continued

420

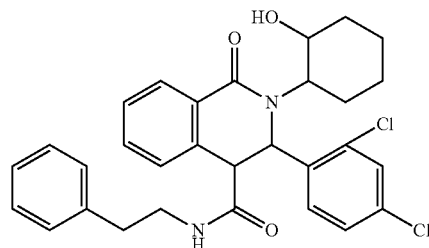
1',2'-cis,
3,4-trans,
racemic
mixture,
less
polar

5

10

15

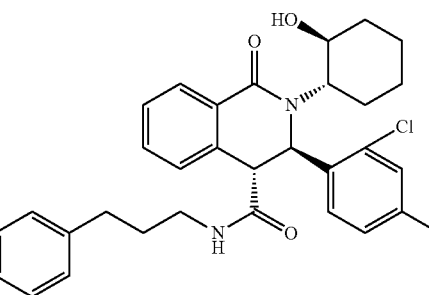
421

1',2'-cis,
3,4-trans,
racemic
mixture,
more
polar

20

25

422

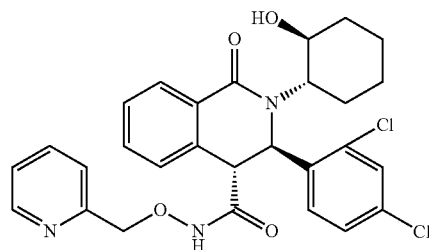
racemic
mixture

30

35

40

423

racemic
mixture

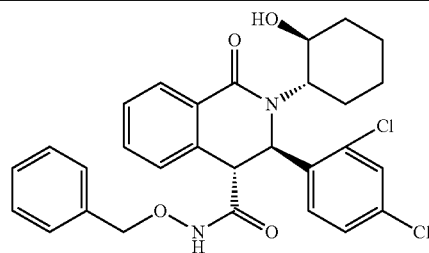
45

50

TABLE 153

55

424

racemic
mixture

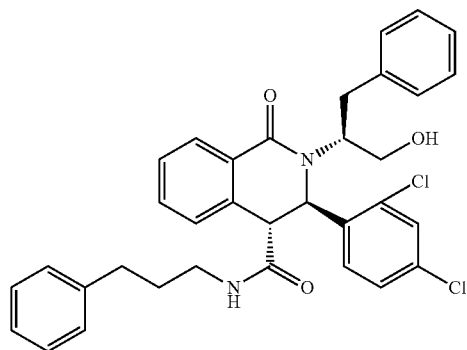
60

65

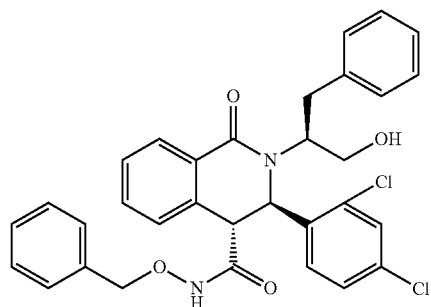
225

TABLE 153-continued

425



426



226

TABLE 153-continued

427

5

10

15

428

20

25

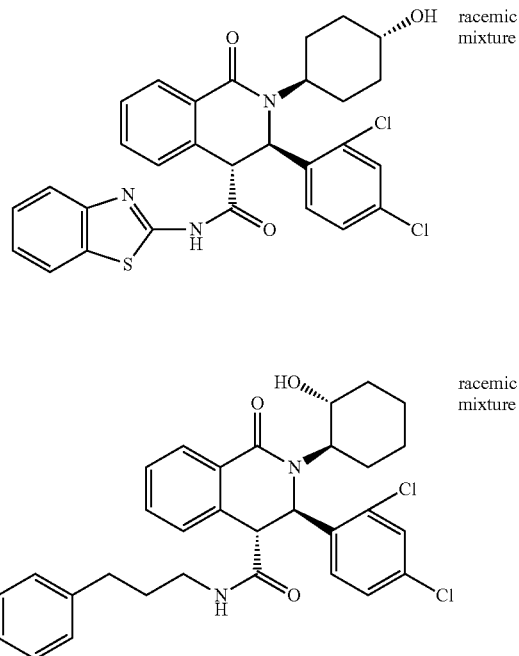
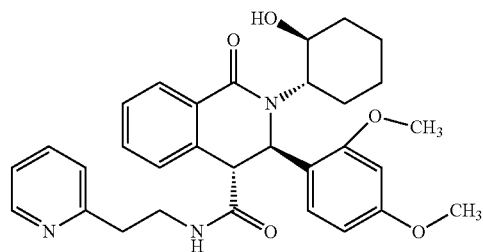


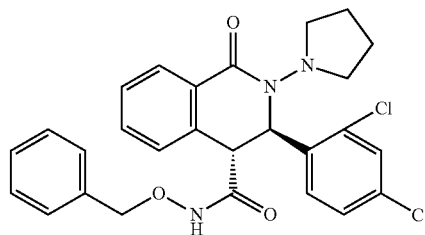
TABLE 154

429



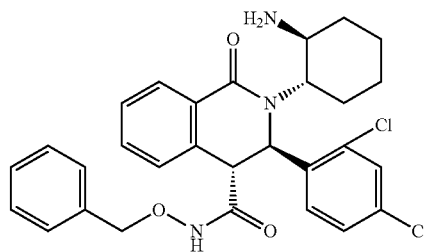
1',2'-trans,
3,4-trans,
diastereomer
of Ex443,
more polar

430



racemic
mixture

431

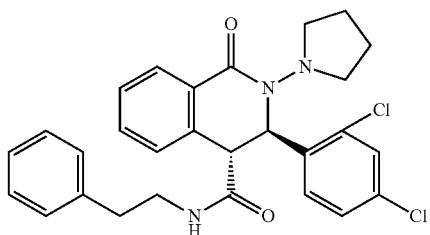


227

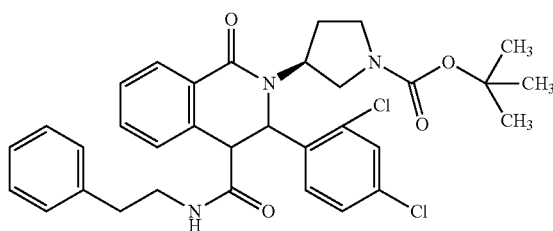
228

TABLE 154-continued

432

racemic
mixture

433

3,4-trans,
diastereo
mixture

434

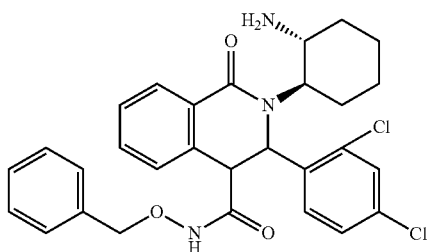
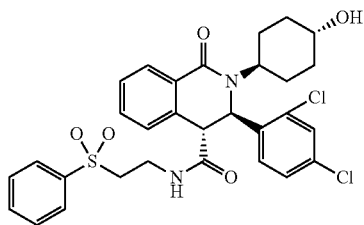
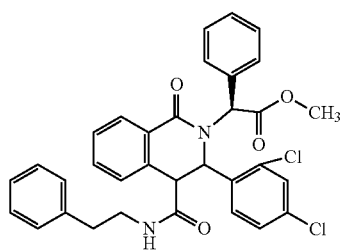
3,4-trans,
diastereo
mixture

TABLE 155

435

racemic
mixture

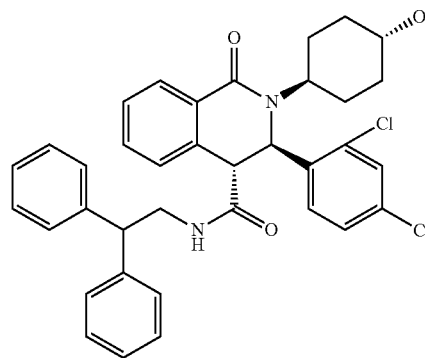
436



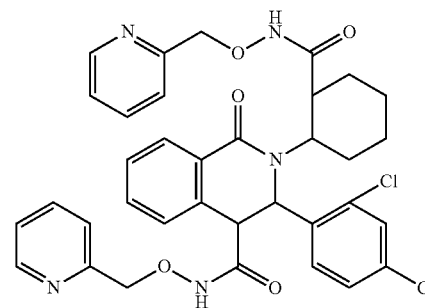
3,4-trans

TABLE 155-continued

40 437

racemic
mixture

55 438

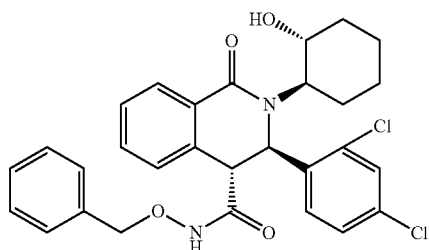
1',2'-trans,
3,4-trans

65

229

TABLE 155-continued

439



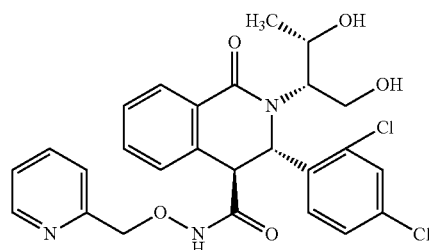
racemic mixture

230

TABLE 157

445

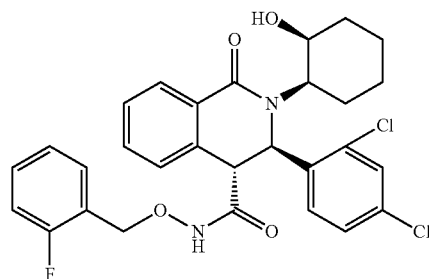
5



10

15

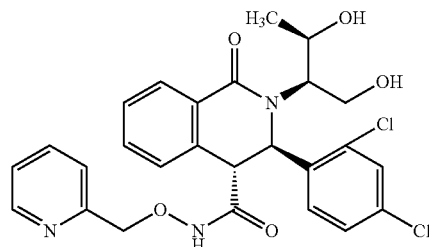
446



25

30

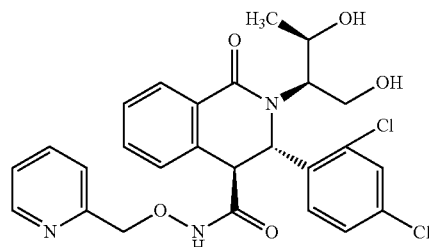
447



35

40

448

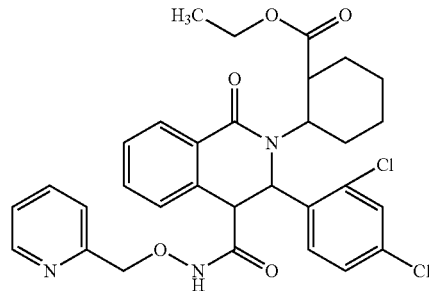


45

50

55

449

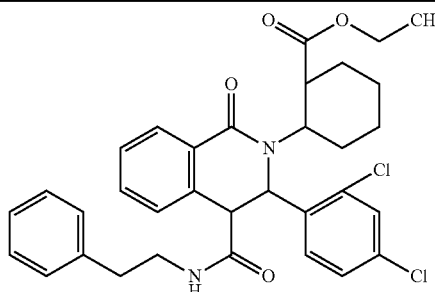


60

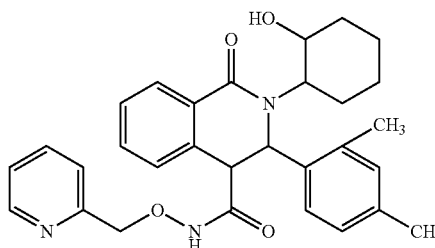
65

TABLE 156

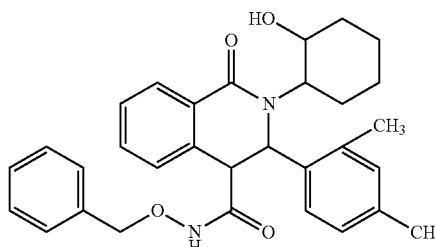
440

1',2'-cis,
3,4-trans,
racemic mixture

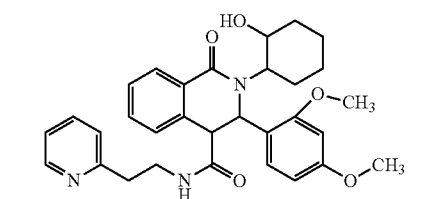
441

1',2'-trans,
3,4-trans
racemic mixture

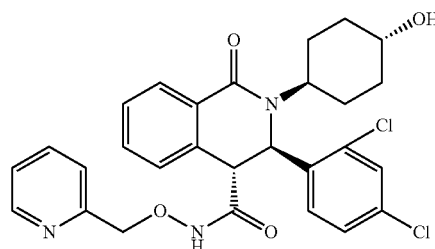
442

1',2'-trans,
3,4-trans

443

1',2'-trans,
3,4-trans
diastereomer
of Ex429,
less polar

444



racemic mixture

231

TABLE 158

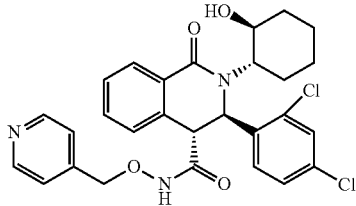
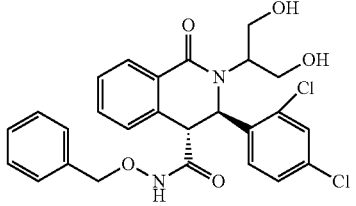
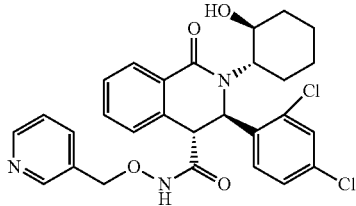
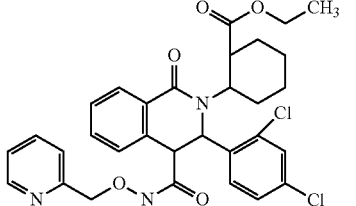
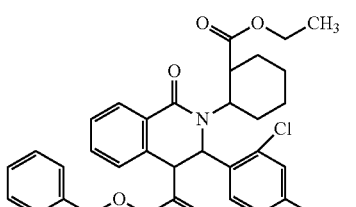
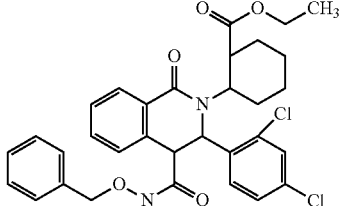
450		racemic mixture
451		racemic mixture
452		racemic mixture
453		1',2'-cis, 3,4-trans, racemic mixture
454		1',2'-cis, 3,4-trans, diastereomer of Ex455

TABLE 159

455		1',2'-cis, 3,4-trans, racemic mixture
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232

TABLE 159-continued

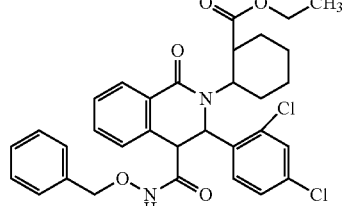
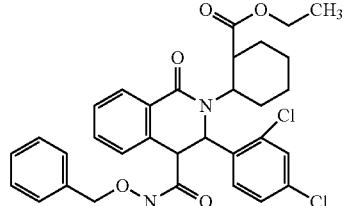
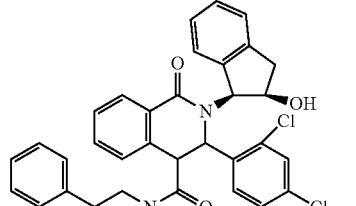
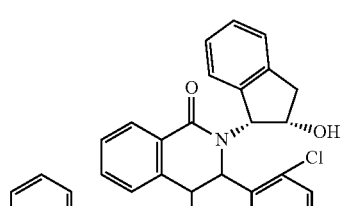
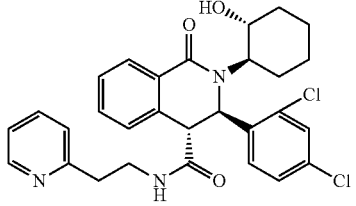
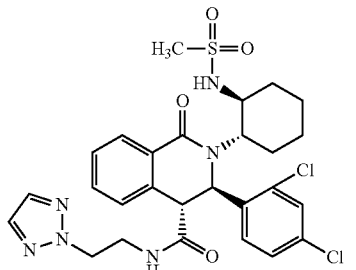
456		1',2'-trans, 3,4-trans
457		1',2'-trans, 3,4-trans, diastereomer of Ex456
458		3,4-trans
459		chiral compound, 3,4-trans

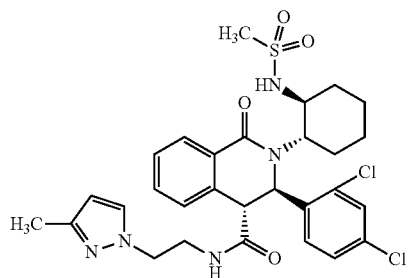
TABLE 160

460		racemic mixture
461		racemic mixture

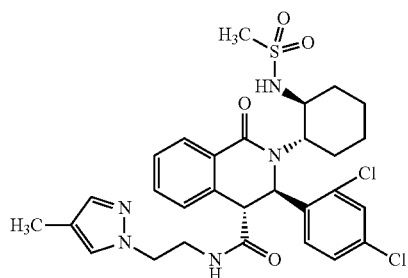
233

TABLE 160-continued

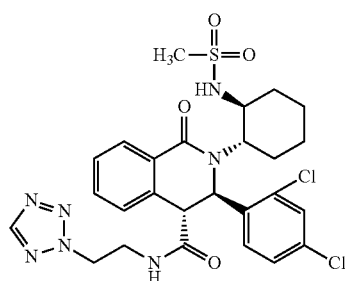
462



3:1 mixture



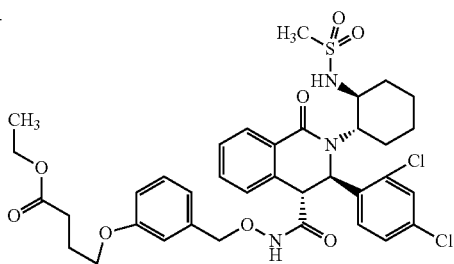
463



racemic mixture

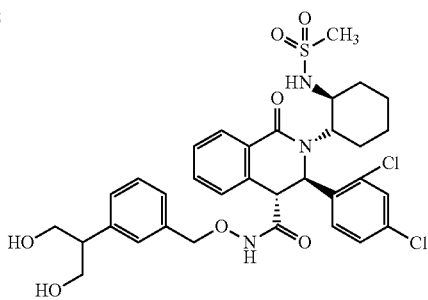
TABLE 161

464



racemic mixture

465

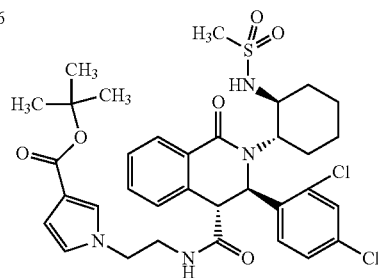


racemic mixture

234

TABLE 161-continued

466



racemic mixture

467

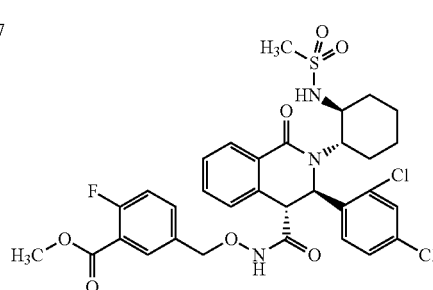
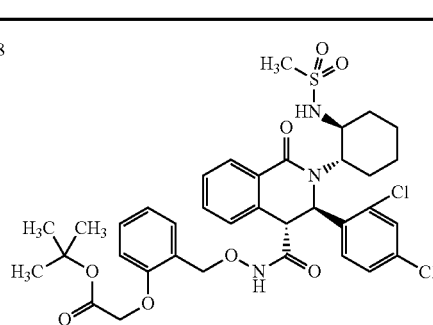


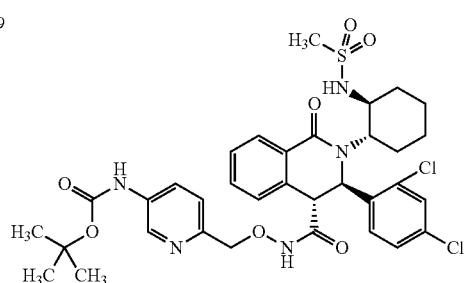
TABLE 162

468



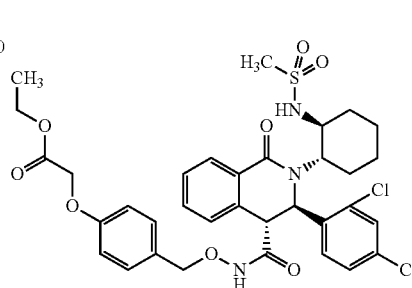
racemic mixture

469



racemic mixture

470



racemic mixture

235

TABLE 162-continued

471

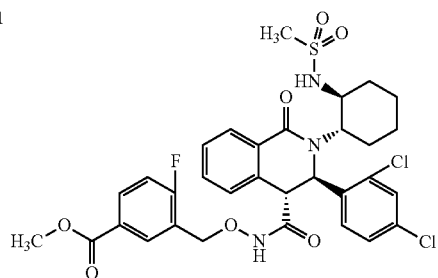
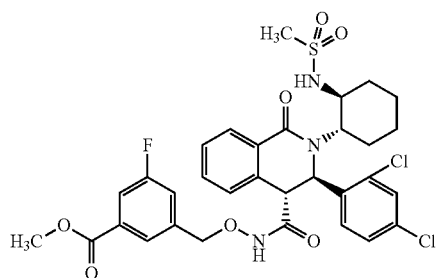
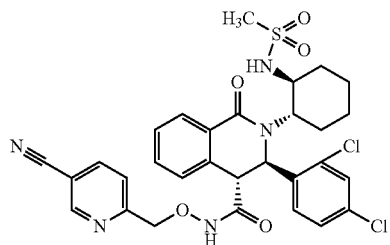
racemic
mixture

TABLE 163

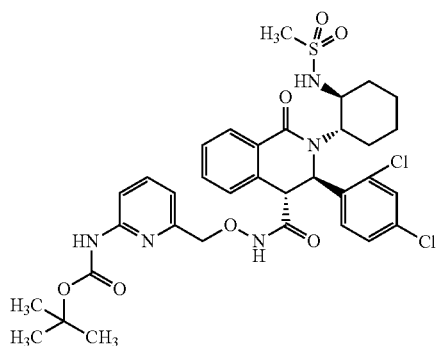
472

racemic
mixture

473

racemic
mixture

474

racemic
mixture

475

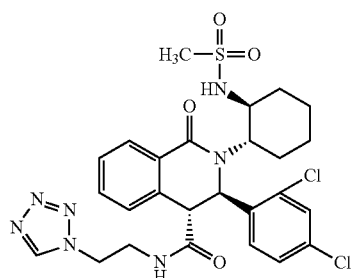
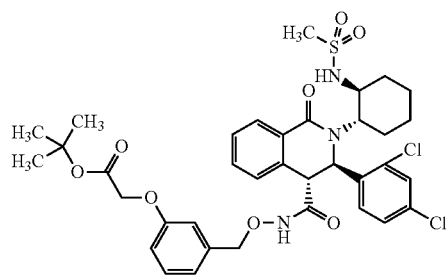
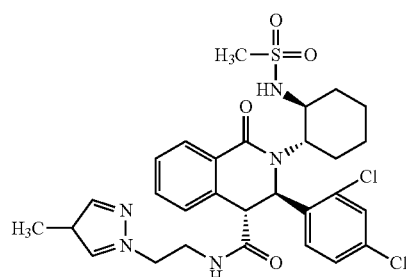
racemic
mixture**236**

TABLE 164

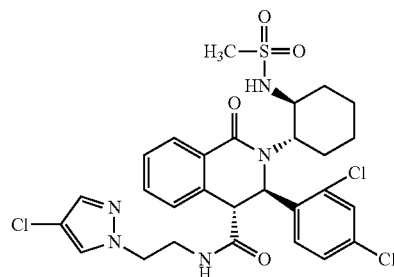
476

racemic
mixture

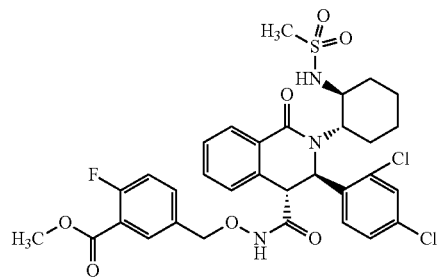
15 477

racemic
mixture

20 478

racemic
mixture

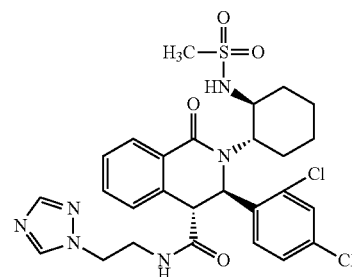
30 479

racemic
mixture

40

TABLE 165

55 480

racemic
mixture

60

237

TABLE 165-continued

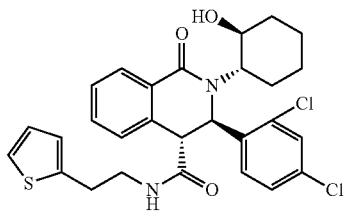
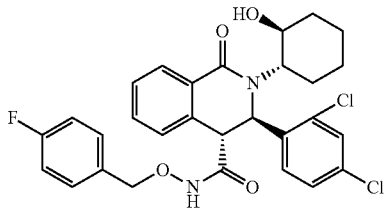
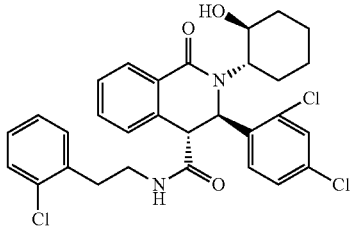
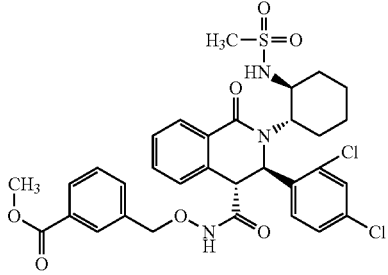
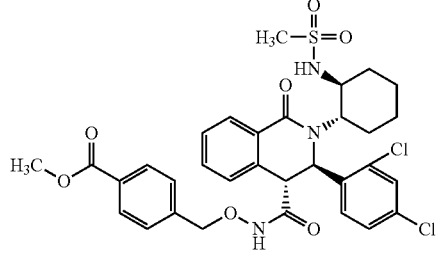
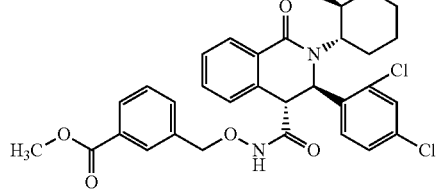
481		racemic mixture
482		racemic mixture
483		racemic mixture
484		racemic mixture

TABLE 166

485		racemic mixture
486		racemic mixture

238

TABLE 166-continued

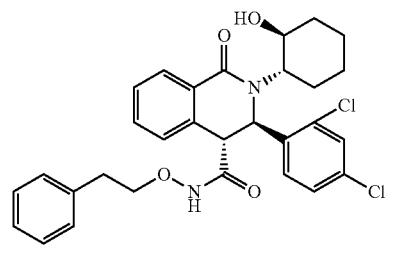
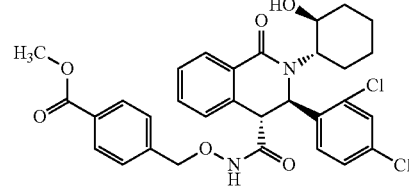
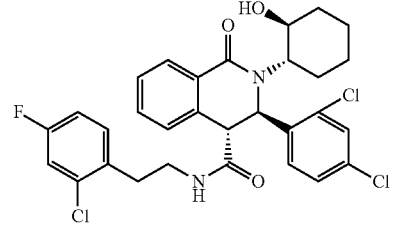
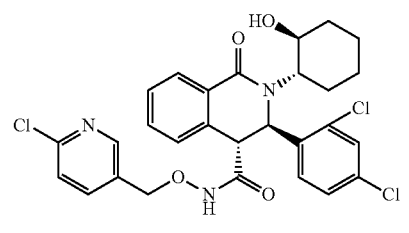
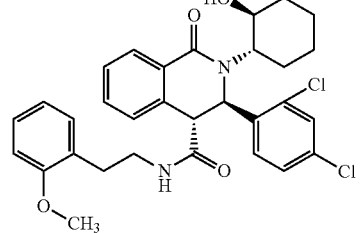
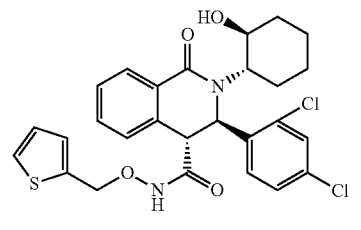
487		racemic mixture
488		racemic mixture
489		racemic mixture

TABLE 167

490		racemic mixture
491		racemic mixture
492		racemic mixture

239

TABLE 167-continued

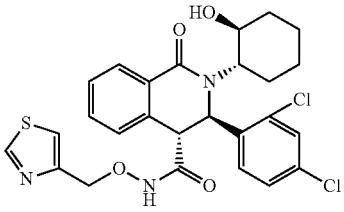
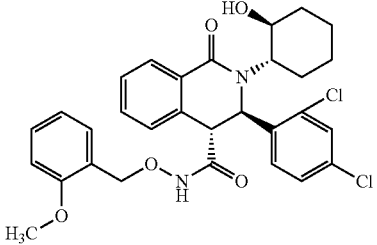
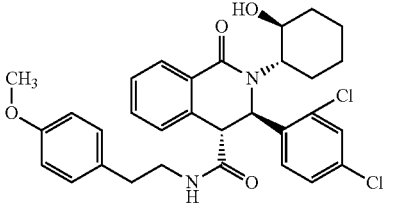
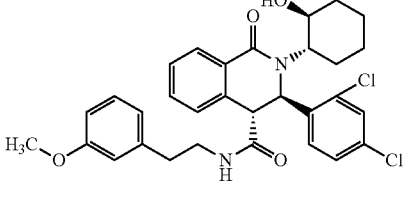
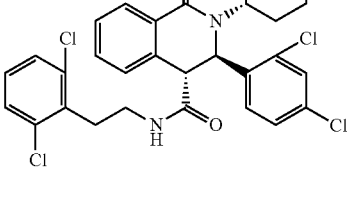
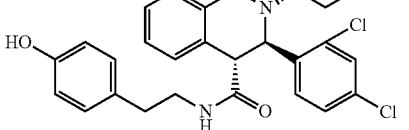
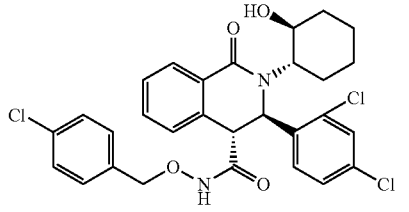
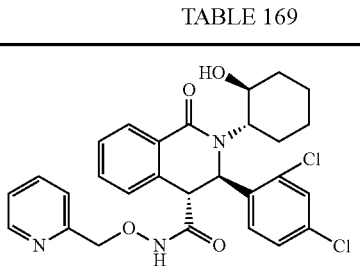
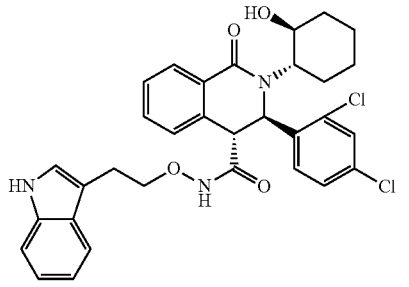
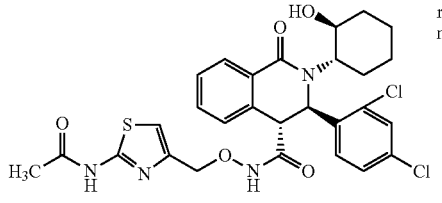
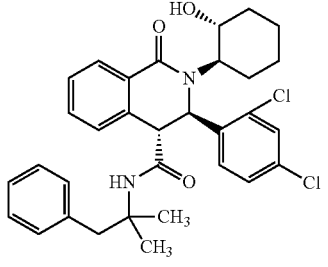
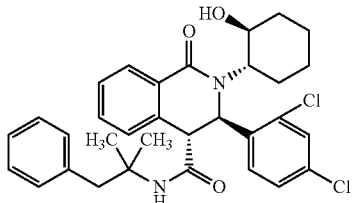
493		racemic mixture
494		racemic mixture

TABLE 168

495		racemic mixture
496		racemic mixture
497		racemic mixture
498		racemic mixture

240

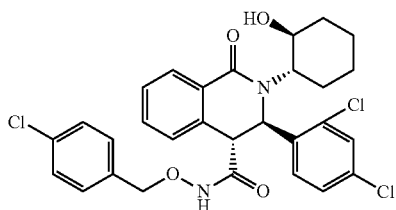
TABLE 168-continued

499		racemic mixture
500	 HCl	racemic mixture
501		racemic mixture
502		racemic mixture
503		racemic mixture
504		racemic mixture

241

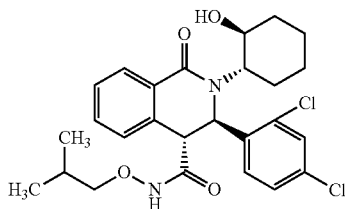
TABLE 170

505



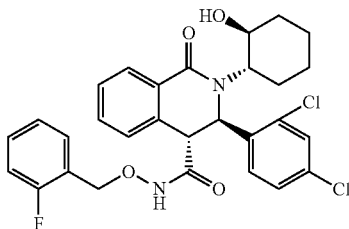
racemic mixture

506



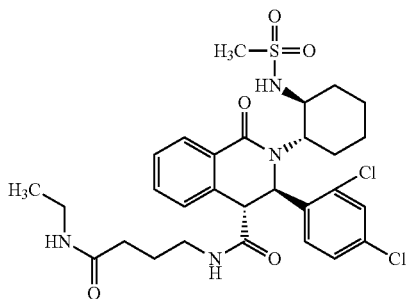
racemic mixture

507



racemic mixture

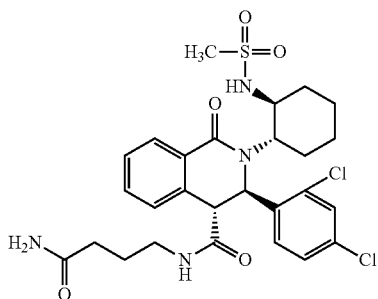
32



racemic mixture

TABLE 171

508

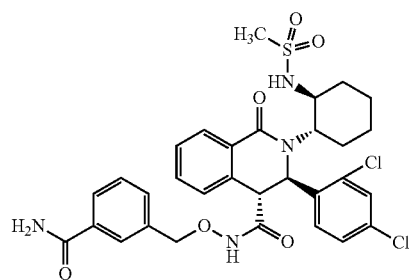


racemic mixture

242

TABLE 171-continued

509



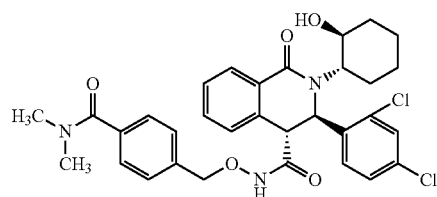
racemic mixture

5

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15

510

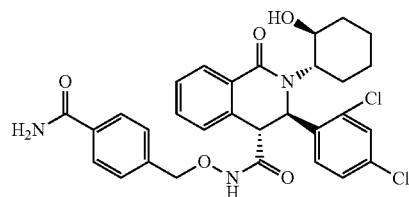


racemic mixture

20

25

511

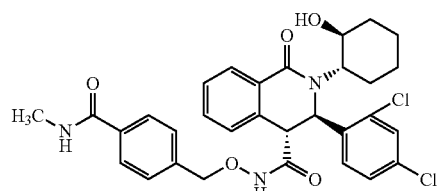


racemic mixture

30

35

512

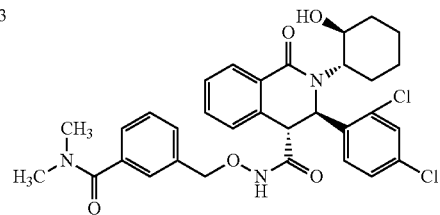


racemic mixture

45

TABLE 172

513

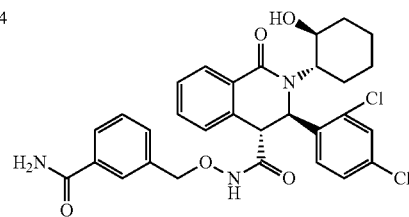


racemic mixture

50

55

514



racemic mixture

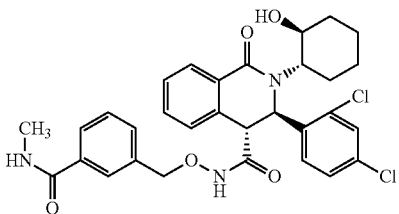
60

65

243

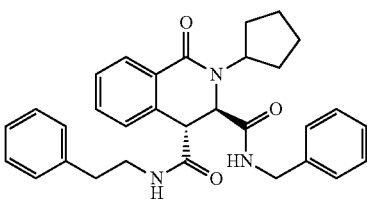
TABLE 172-continued

515

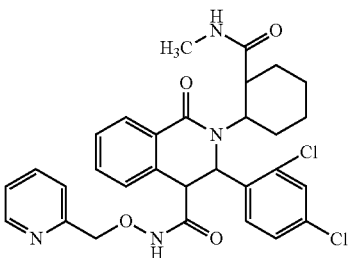


racemic
mixture

33

racemic
mixture

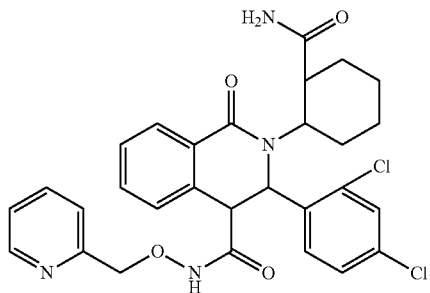
516



1',2'-trans,
3,4-trans

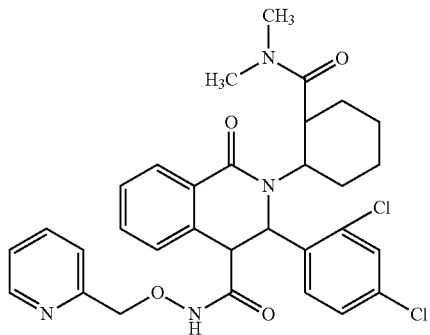
TABLE 173

517



1',2'-trans,
3,4-trans

518

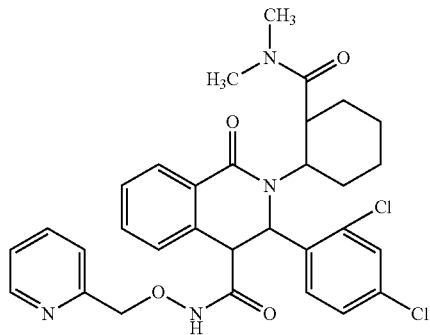


1',2'-trans,
3,4-trans,
diaster-
eomer
of Ex 519

244

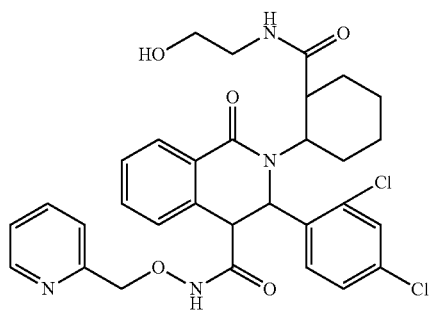
TABLE 173-continued

519



1',2'-trans,
3,4-trans,
diaster-
eomer
of Ex 518

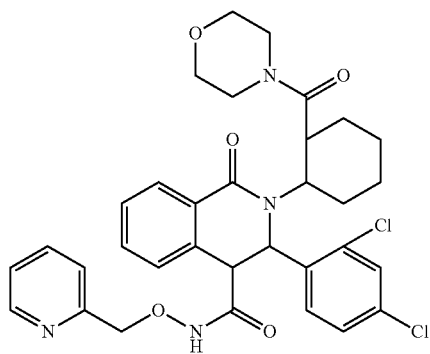
520



1',2'-trans,
3,4-trans

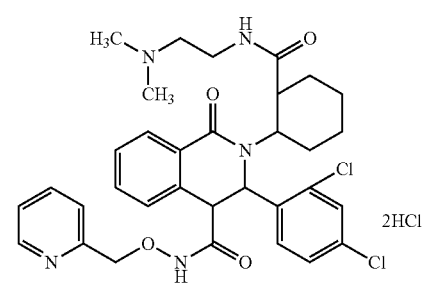
TABLE 174

521



1',2'-trans,
3,4-trans

522



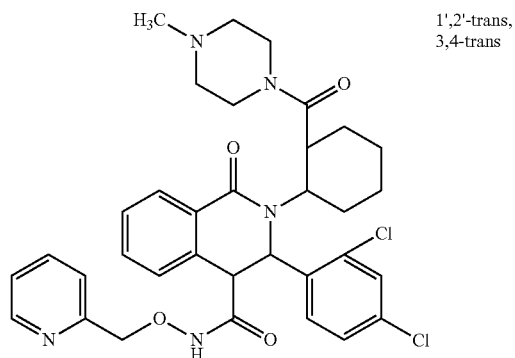
1',2'-trans,
3,4-trans

 2HCl

245

TABLE 174-continued

523



524

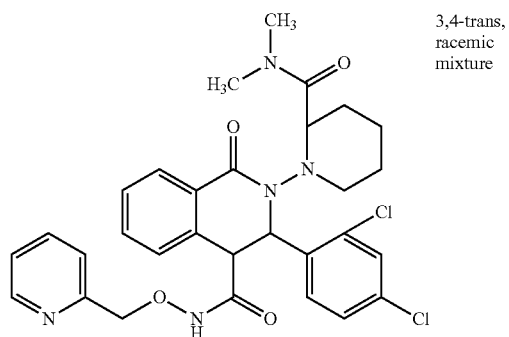
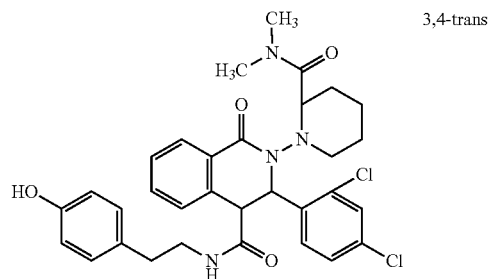
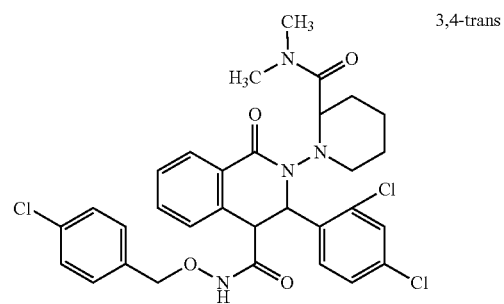


TABLE 175

525



526



246

TABLE 175-continued

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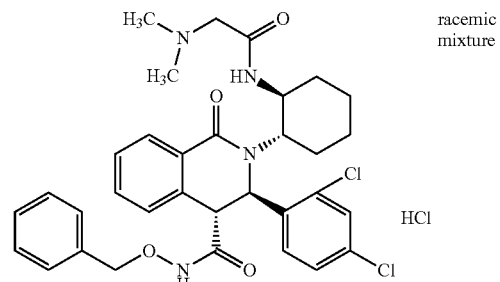
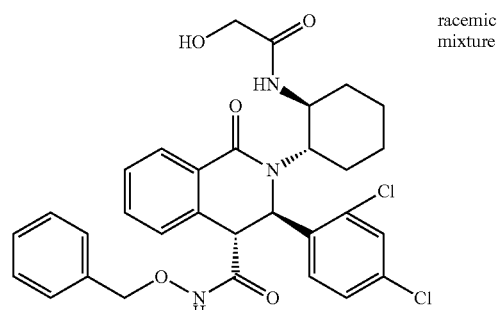


TABLE 176

528

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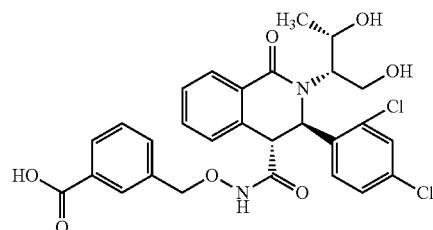
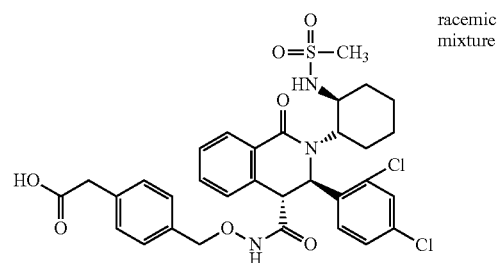
50

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529

60

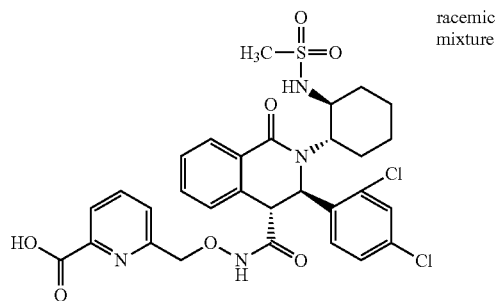
65



247

TABLE 176-continued

530



531

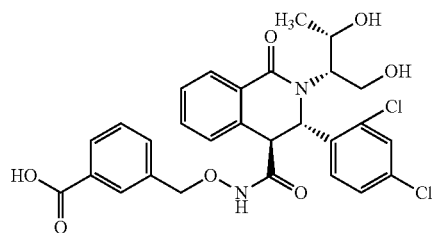


TABLE 177

532

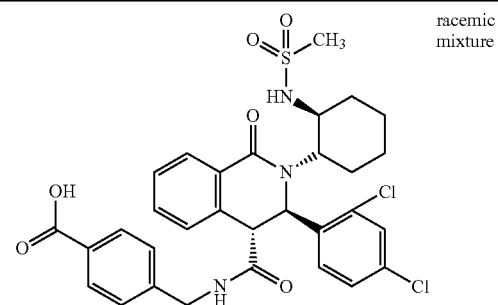
**248**

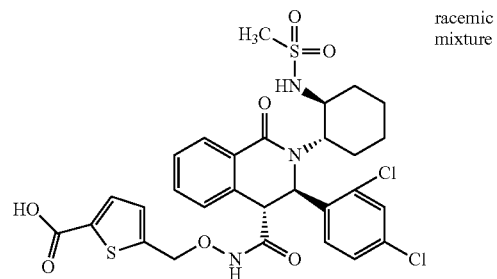
TABLE 177-continued

533

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10

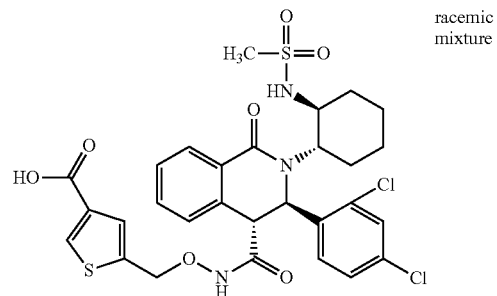
15



20 534

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535

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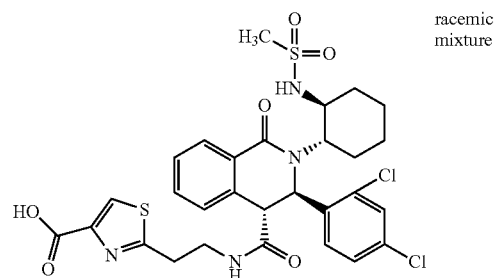


TABLE 178

536

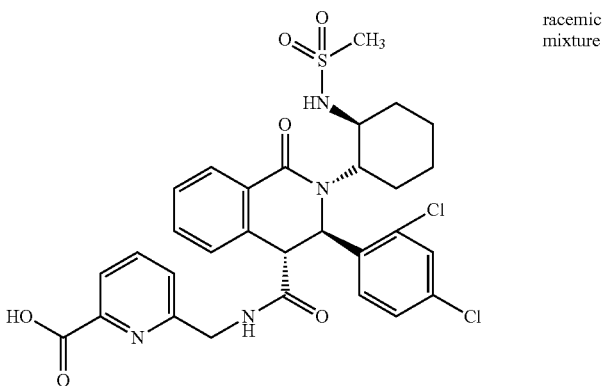
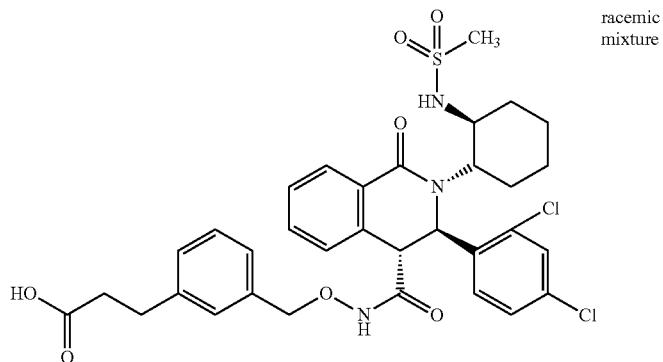
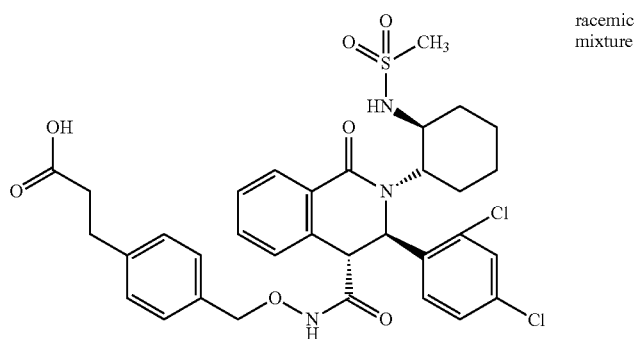


TABLE 178-continued

537



538



539

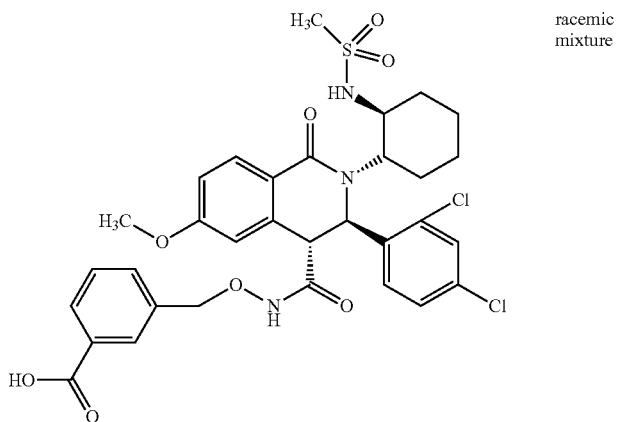


TABLE 179

540

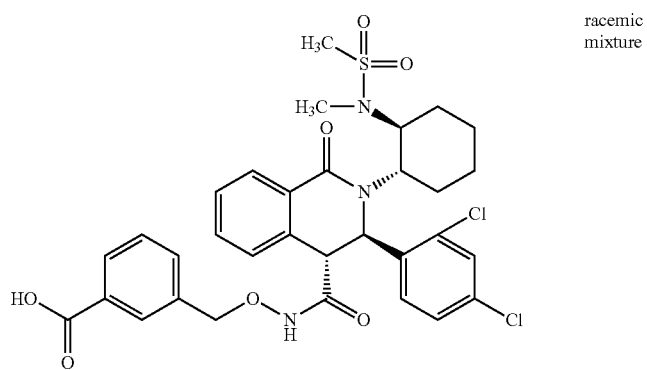
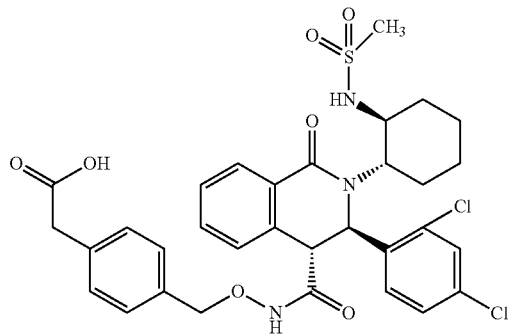
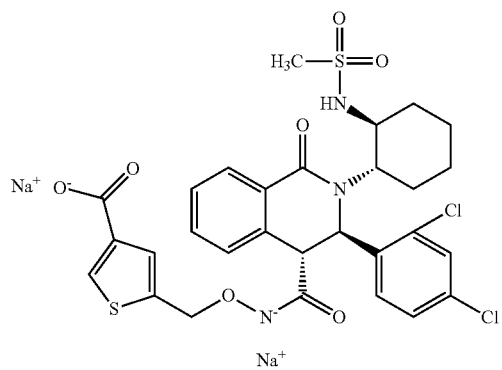


TABLE 179-continued

541



542



543

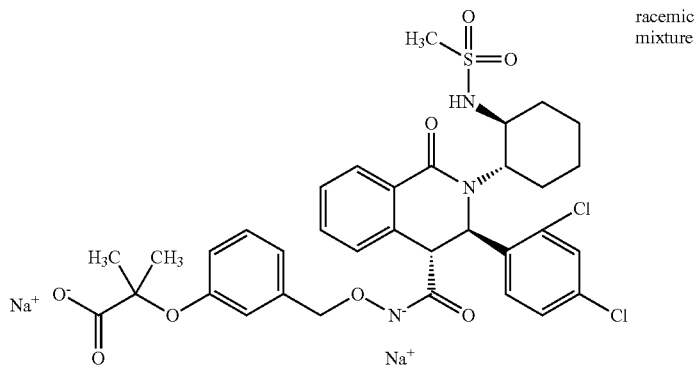


TABLE 180

544

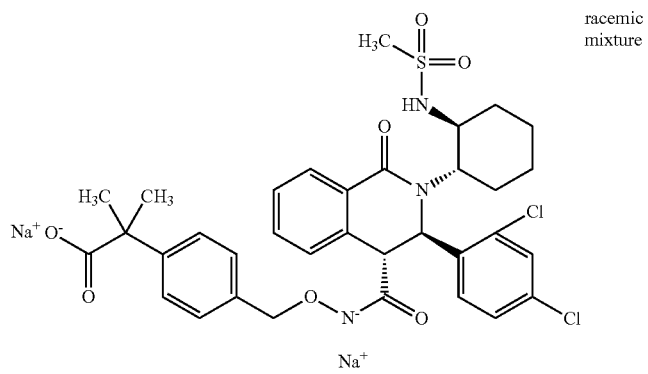
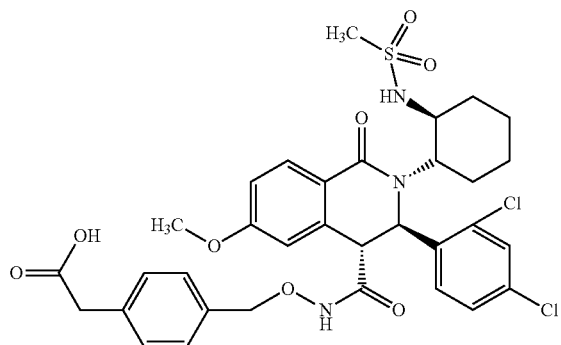
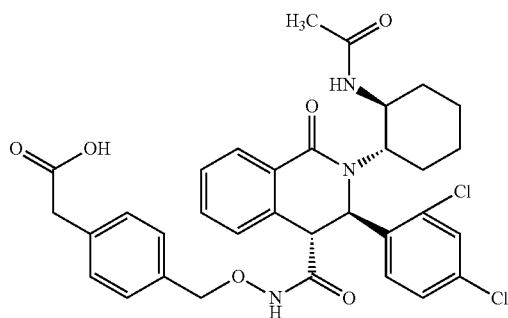


TABLE 180-continued

545

racemic
mixture

546

racemic
mixture

547

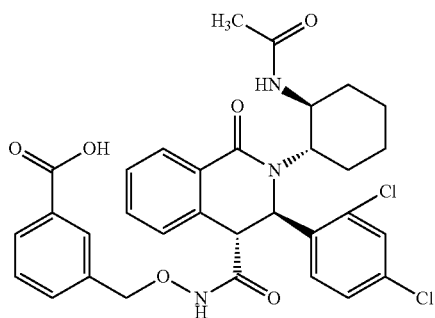
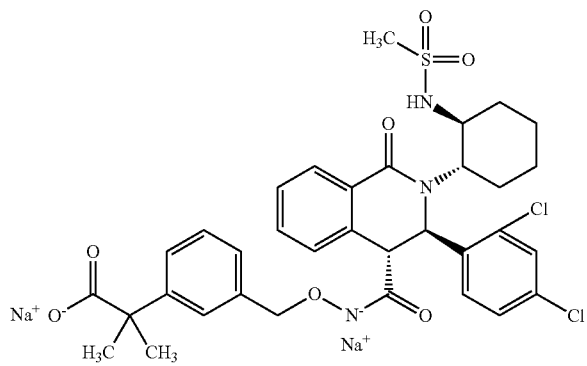
racemic
mixture

TABLE 181

548

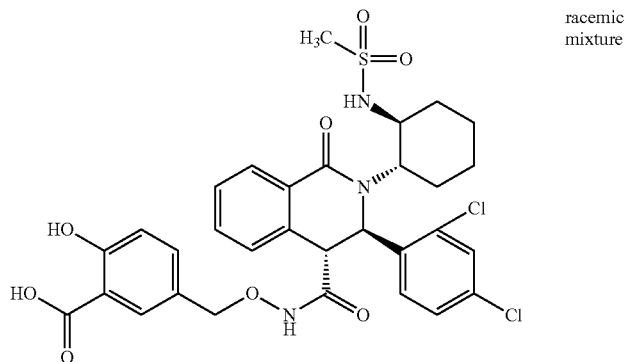
racemic
mixture

255

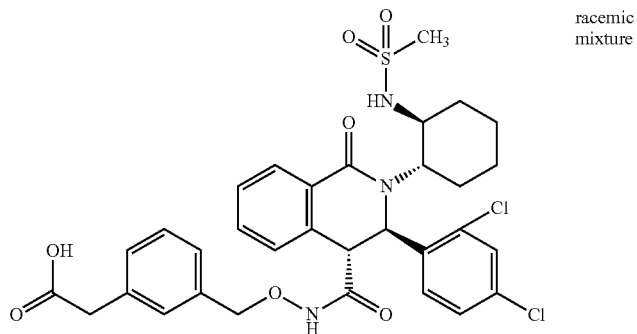
256

TABLE 181-continued

549



550



551

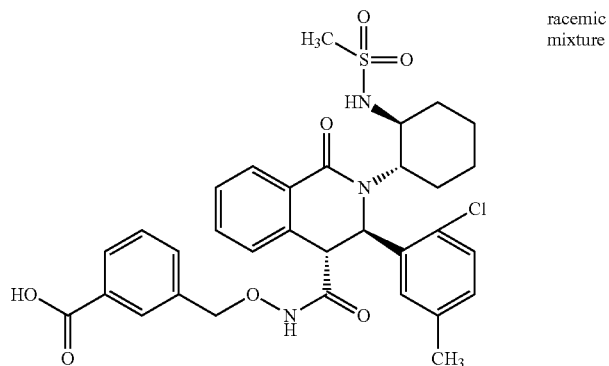


TABLE 182

552

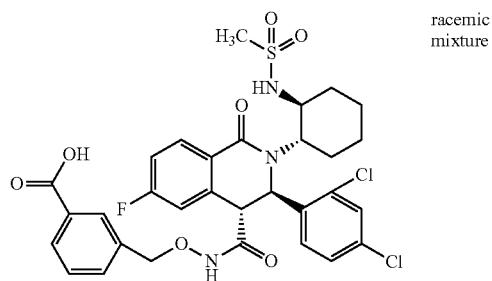
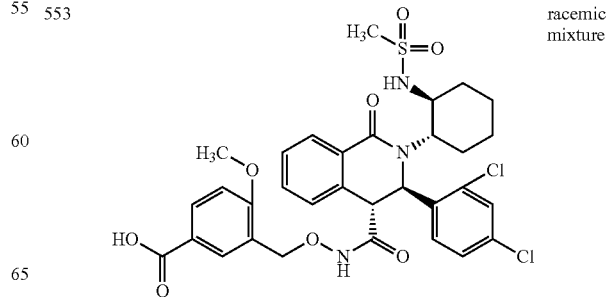


TABLE 182-continued

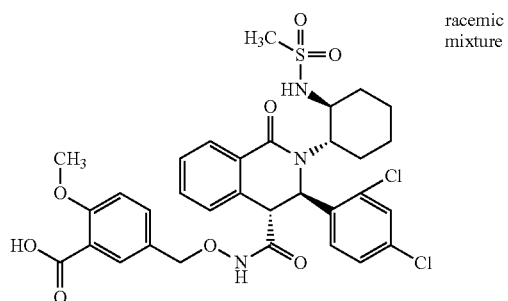
55 553



257

TABLE 182-continued

554



555

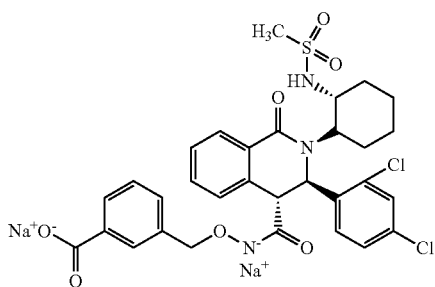
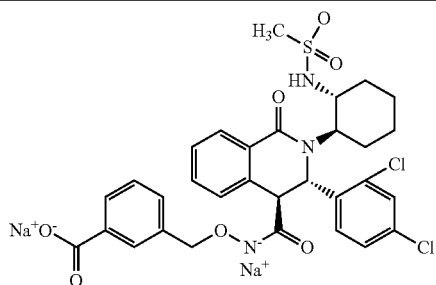
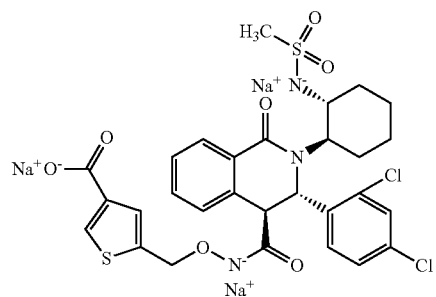


TABLE 183

556



557



558

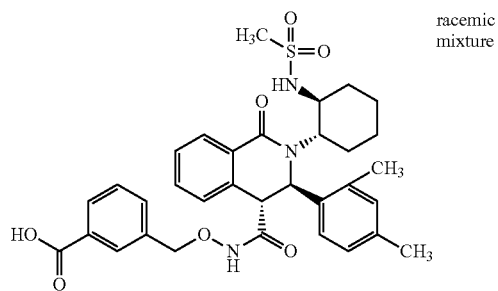
**258**

TABLE 183-continued

559

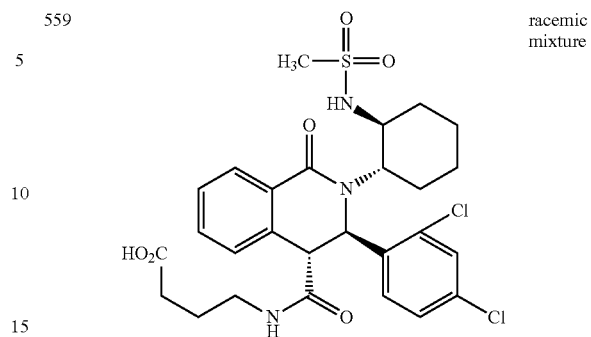
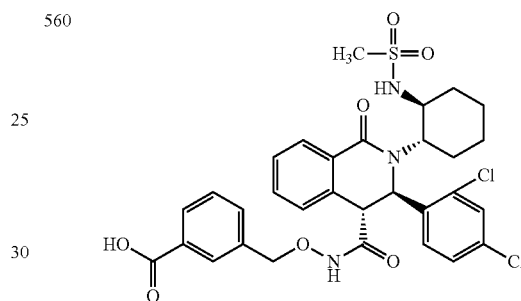
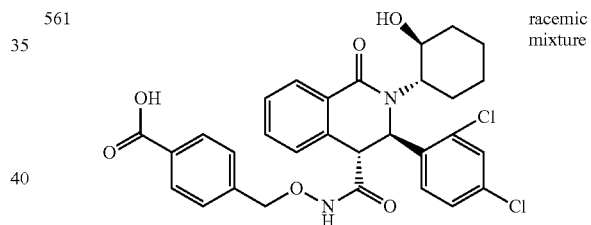


TABLE 184

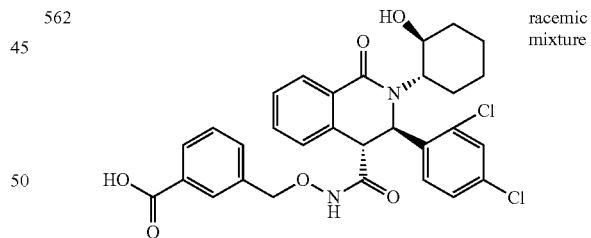
560



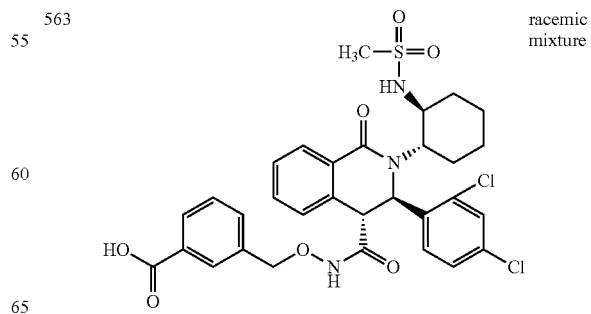
561



562



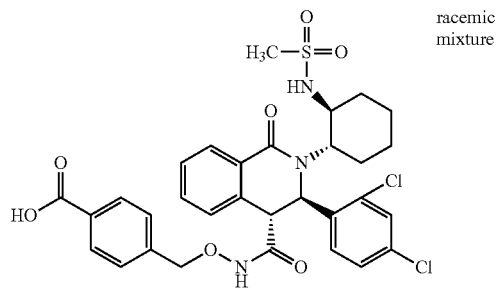
563



259

TABLE 185

564



565

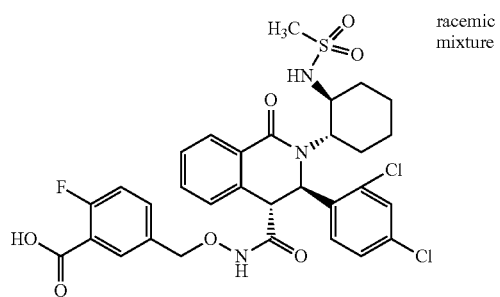
**260**

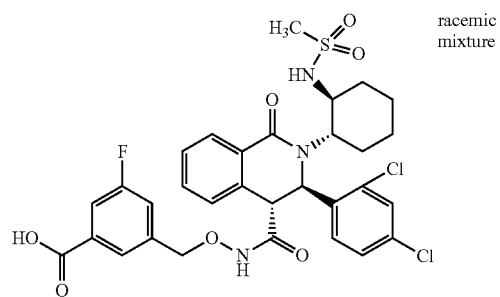
TABLE 185-continued

566

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567

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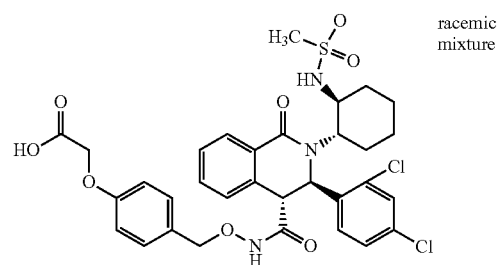
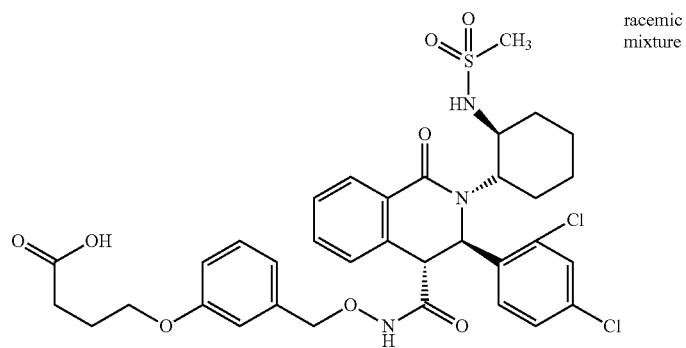
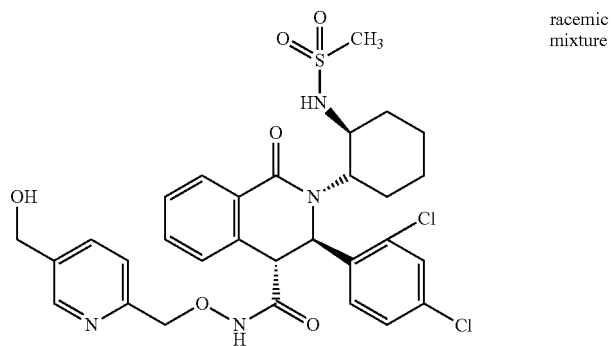


TABLE 186

568



569

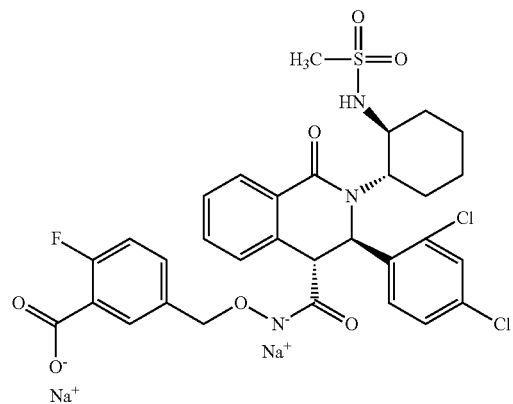


261

262

TABLE 186-continued

570



571

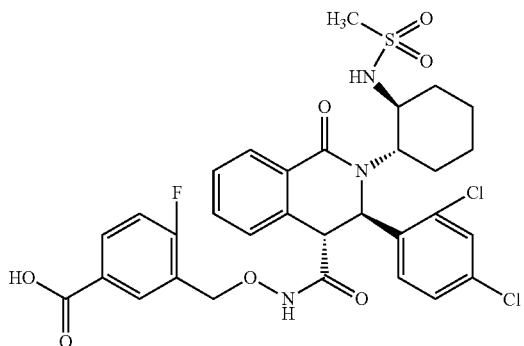
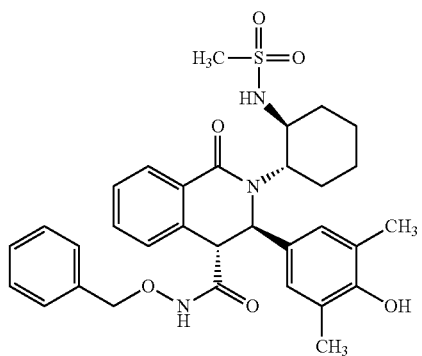
racemic
mixture

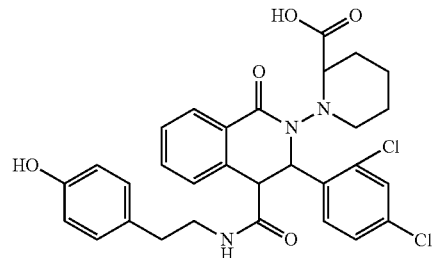
TABLE 187

TABLE 187-continued

572

racemic
mixture

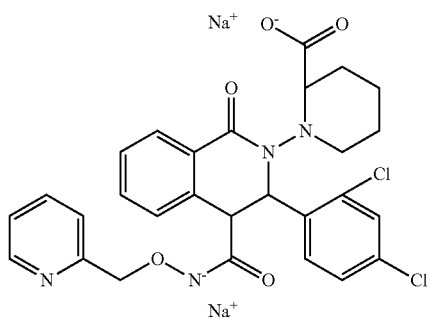
40 574

racemic
mixture

45

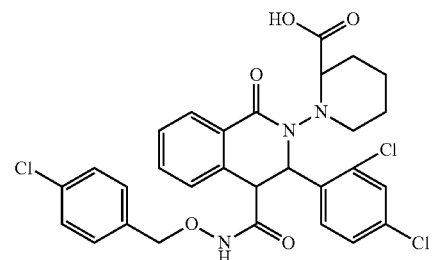
50

573

3,4-trans
racemic
mixture

55

575

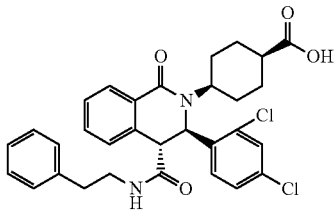
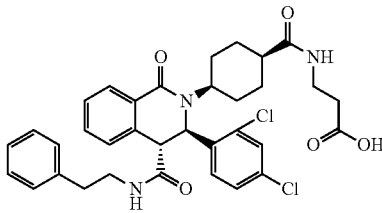
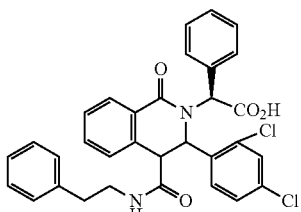
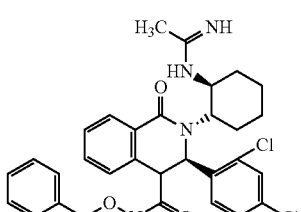
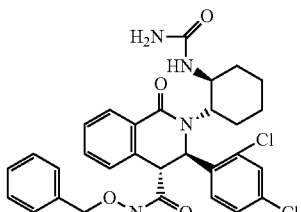
racemic
mixture

60

65

263

TABLE 188

576		racemic mixture
577		racemic mixture
578		3,4-trans
16		racemic mixture
15		racemic mixture

264

TABLE 189

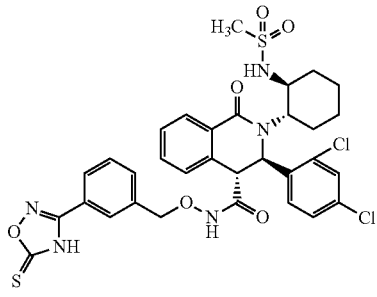
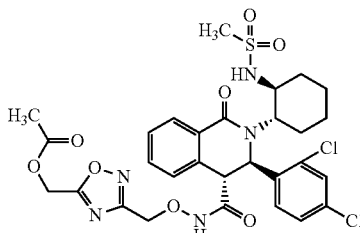
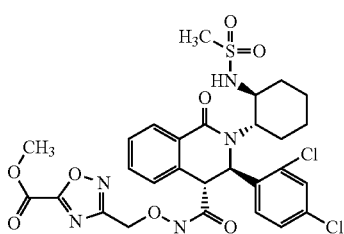
22		racemic mixture
43		racemic mixture
29		racemic mixture

TABLE 190

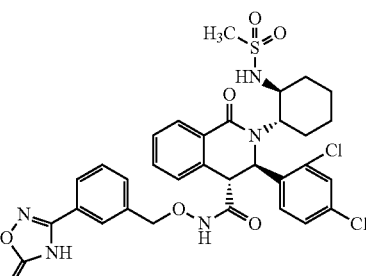
23		racemic mixture
----	--	-----------------

TABLE 190-continued

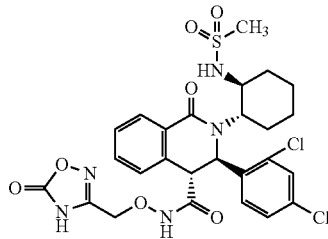
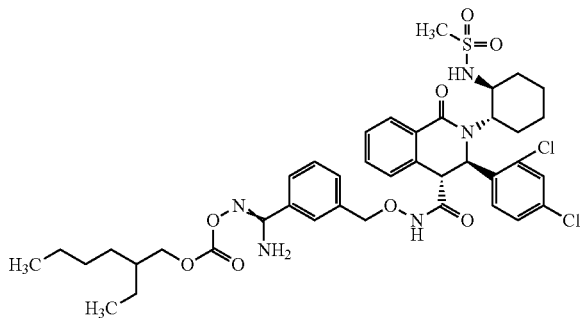
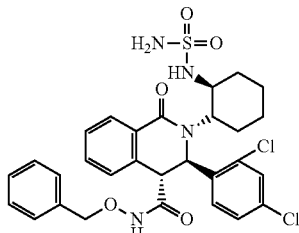
41		racemic mixture
579		racemic mixture
13		racemic mixture

TABLE 191

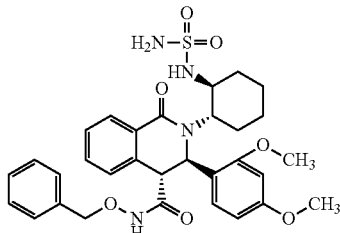
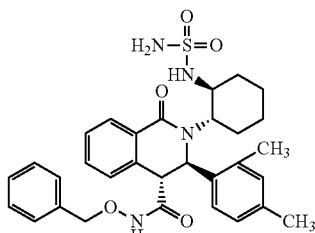
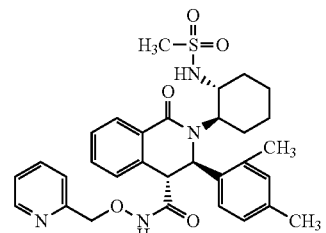
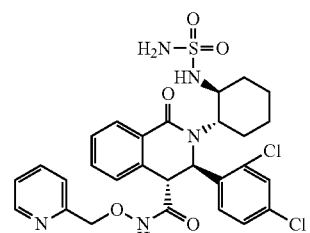
580		racemic mixture
581		racemic mixture, diastereomer of Ex582, less polar

TABLE 191-continued

45	582		racemic mixture, diastereomer of Ex581, more polar
50	583		racemic mixture
55	60		
65			

267

TABLE 192

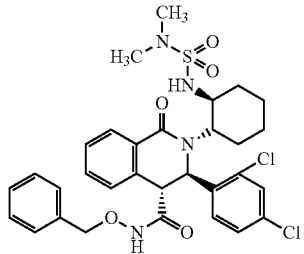
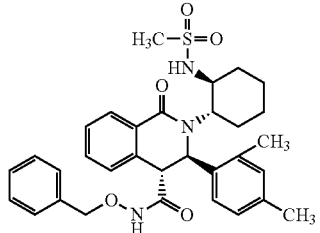
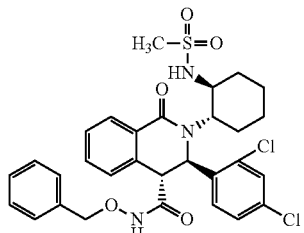
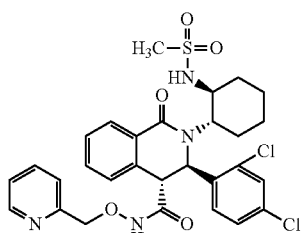
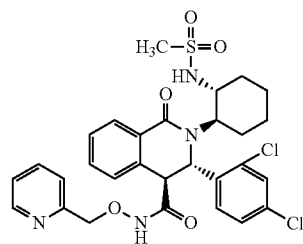
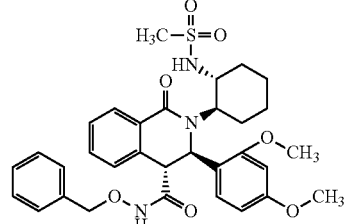
14		racemic mixture
584		racemic mixture
12		racemic mixture
585		racemic mixture

TABLE 193

586		
587		diastereomer of Ex594, less polar

268

TABLE 193-continued

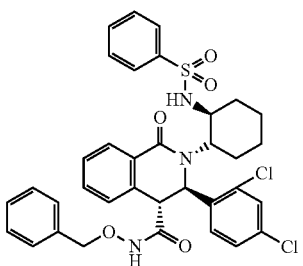
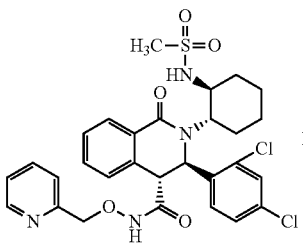
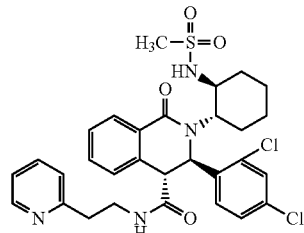
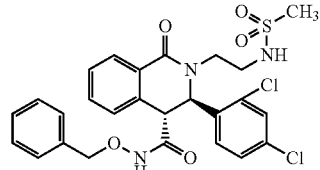
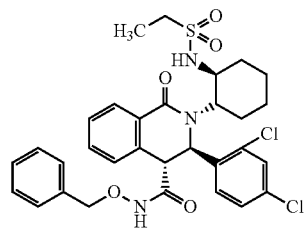
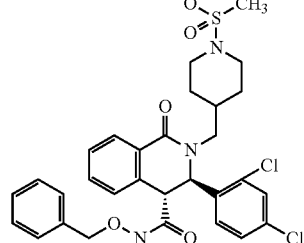
588		racemic mixture
589		HCl

TABLE 194

590		racemic mixture
591		racemic mixture
592		racemic mixture
593		racemic mixture

269

TABLE 195

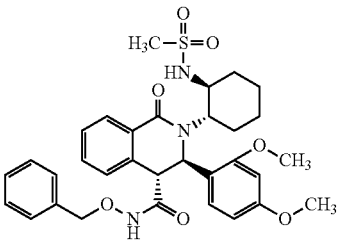
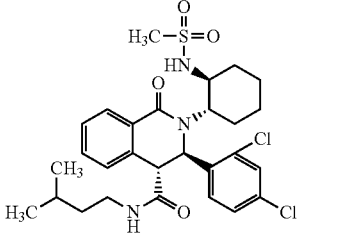
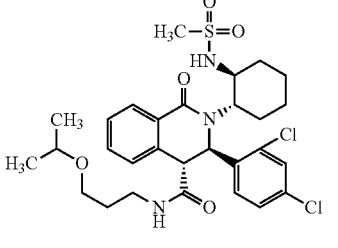
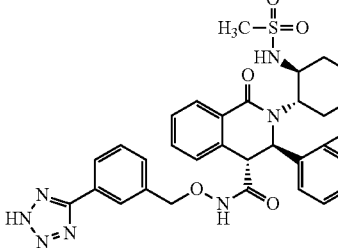
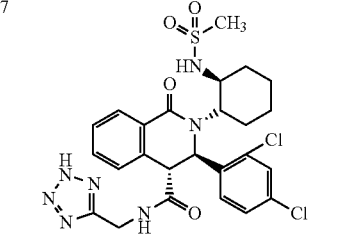
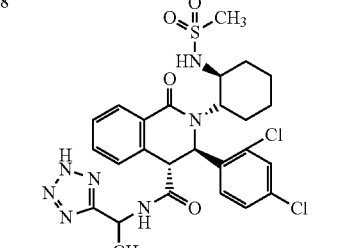
594		diastereomer of Ex587, more polar
595		racemic mixture
596		racemic mixture
18		racemic mixture

TABLE 196

597		racemic mixture
598		chiral compound, diastereomer of Ex599

270

TABLE 196-continued

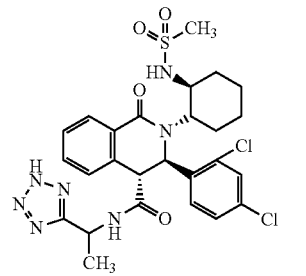
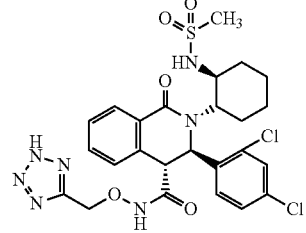
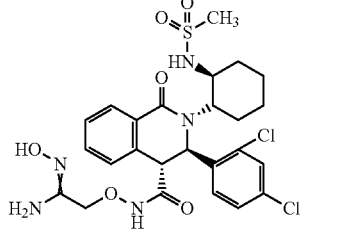
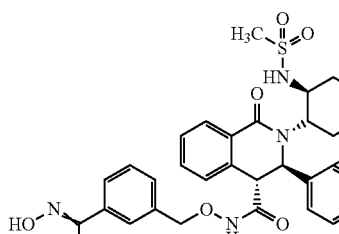
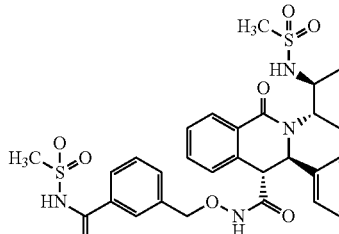
599		chiral compound, diastereomer of Ex598
600		racemic mixture

TABLE 197

21		racemic mixture
601		racemic mixture
20		racemic mixture

271

TABLE 197-continued

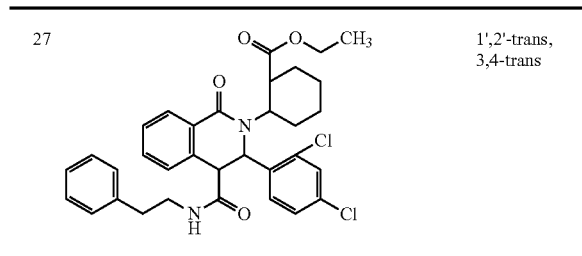


TABLE 198

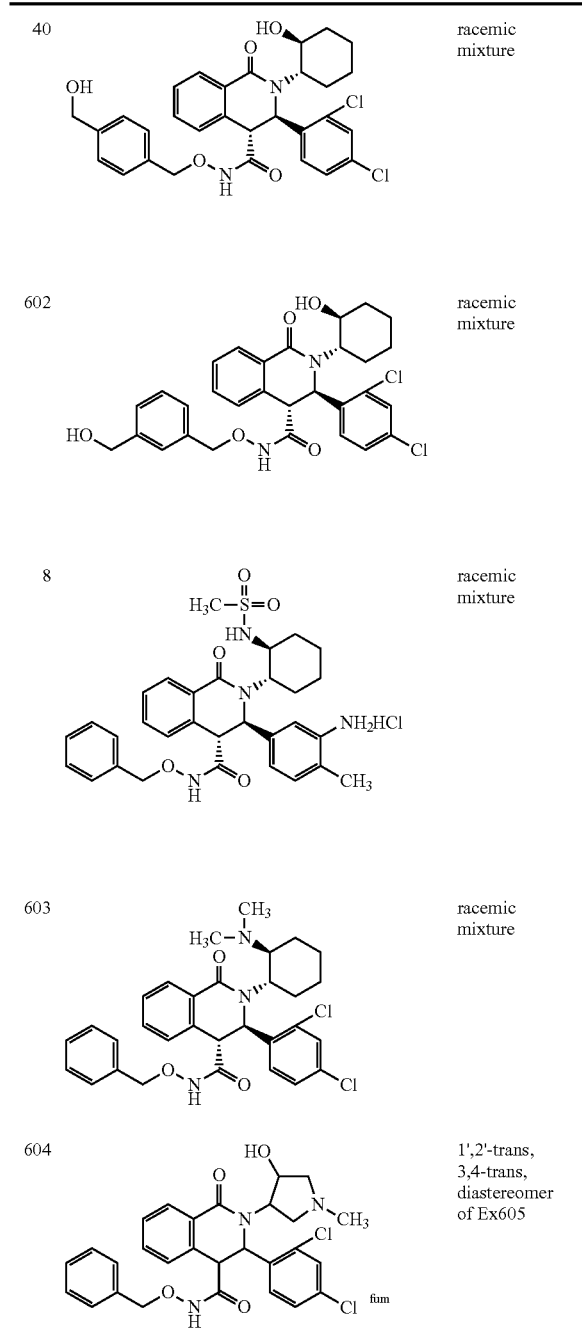
**272**

TABLE 199

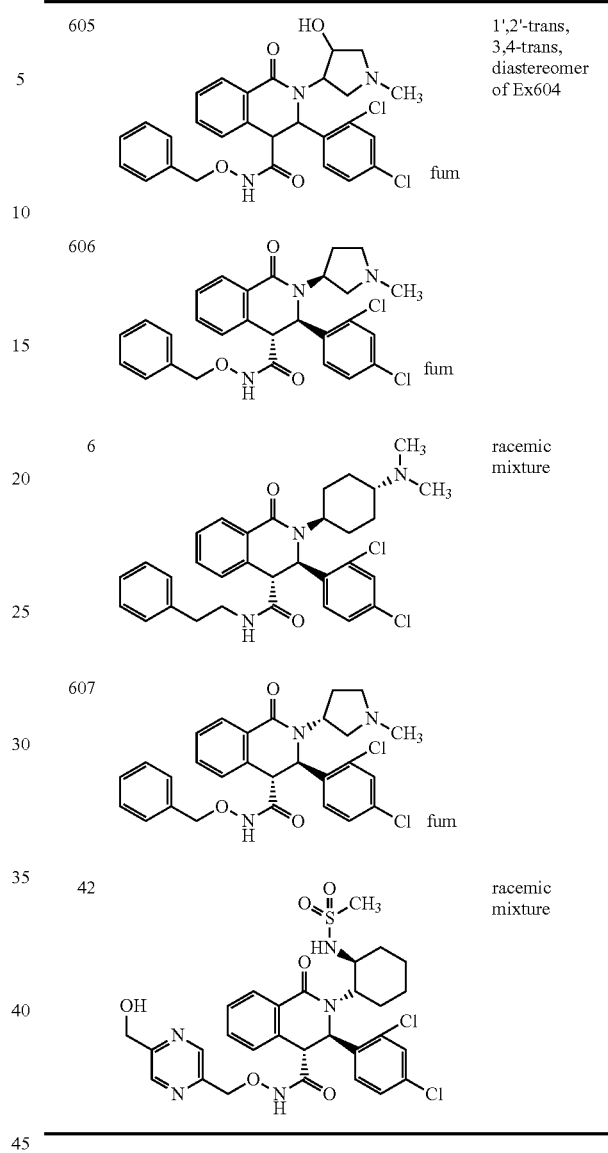
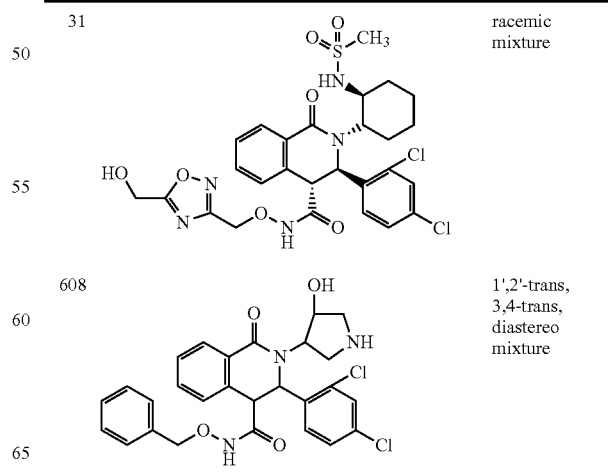


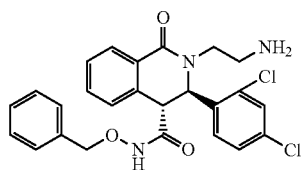
TABLE 200



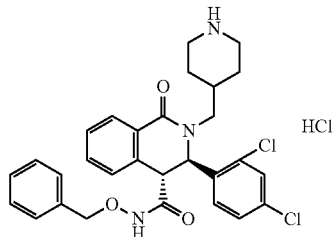
273

TABLE 200-continued

609 racemic mixture



610 racemic mixture



611 1',2'-trans, 3,4-trans, diastereomer of Ex616

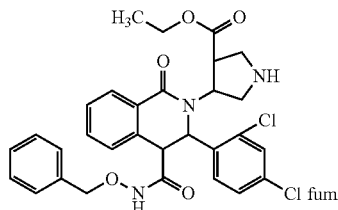


TABLE 201

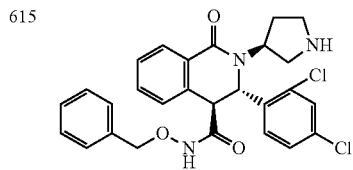
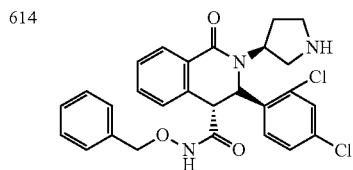
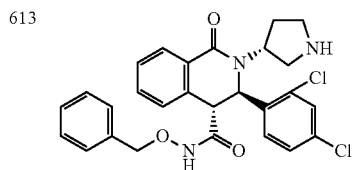
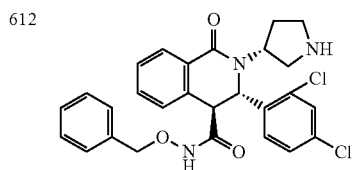
**274**

TABLE 201-continued

616 1',2'-trans, 3,4-trans, diastereomer of Ex611

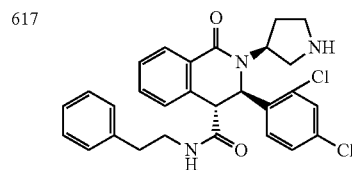
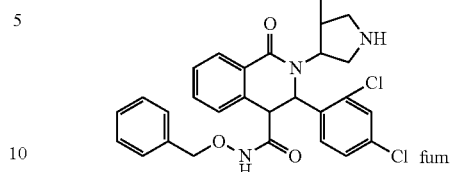
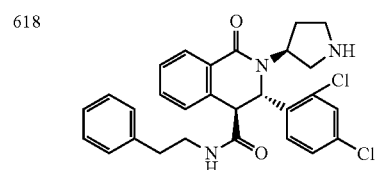
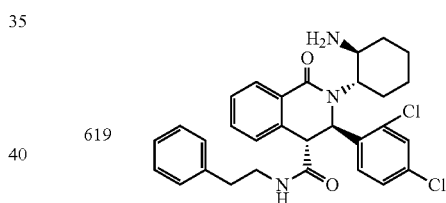


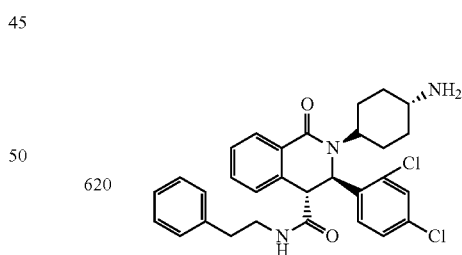
TABLE 202



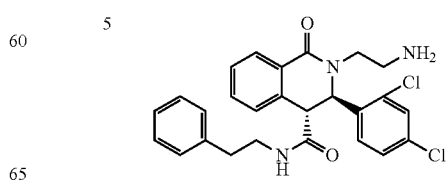
619 racemic mixture



620 racemic mixture



5 racemic mixture



275

TABLE 202-continued

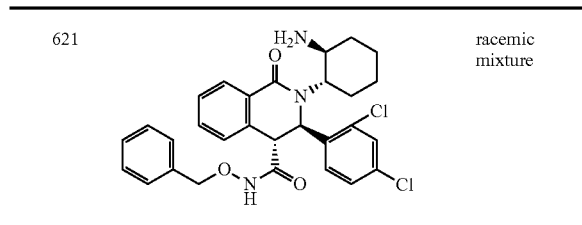


TABLE 203

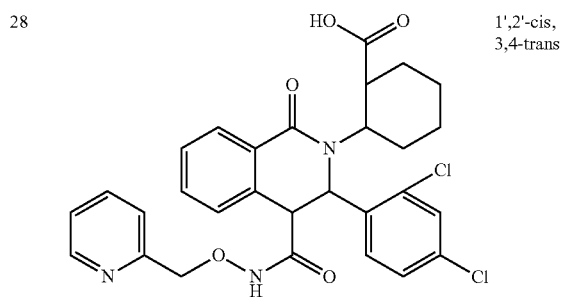
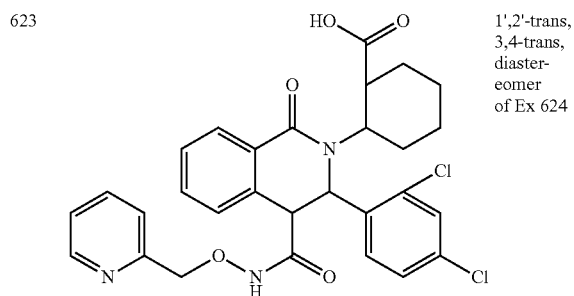
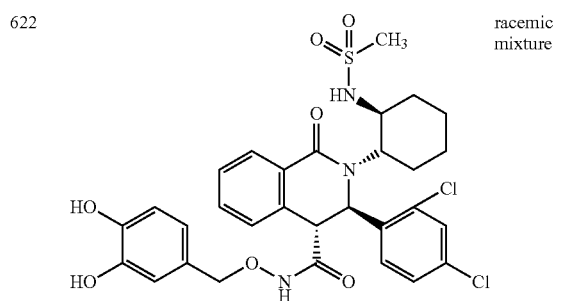
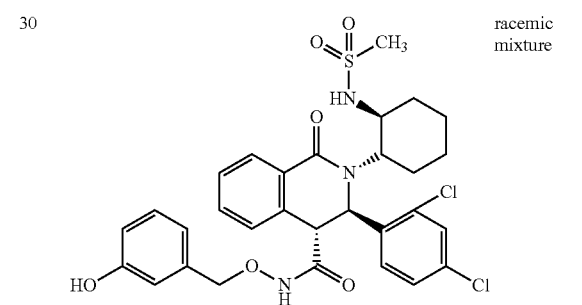
**276**

TABLE 203-continued

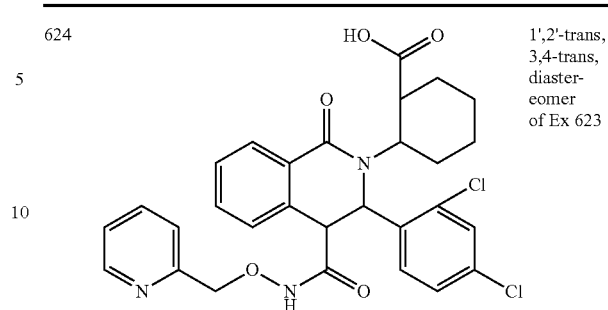
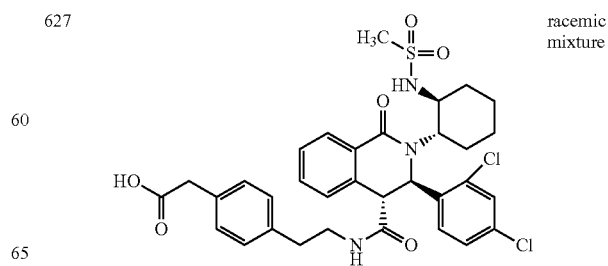
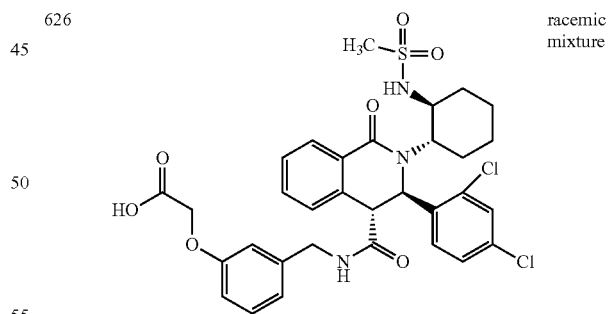
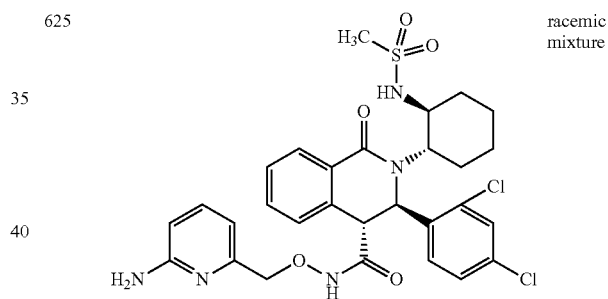
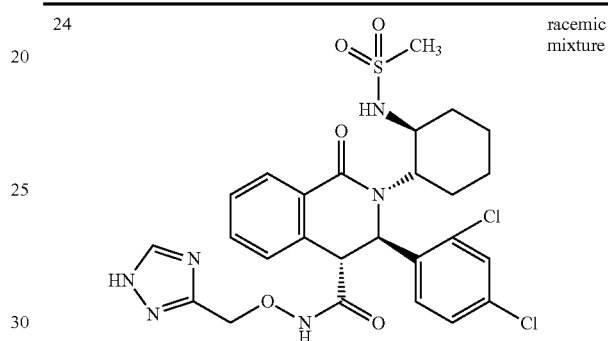
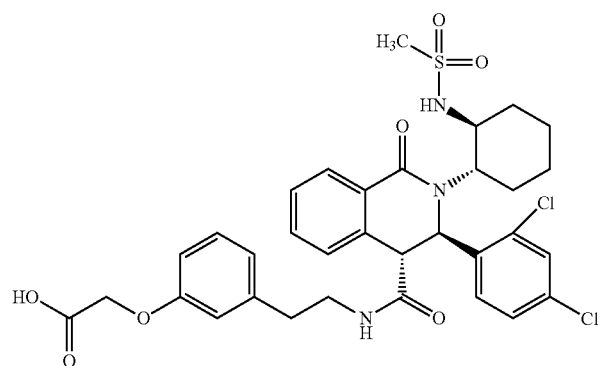


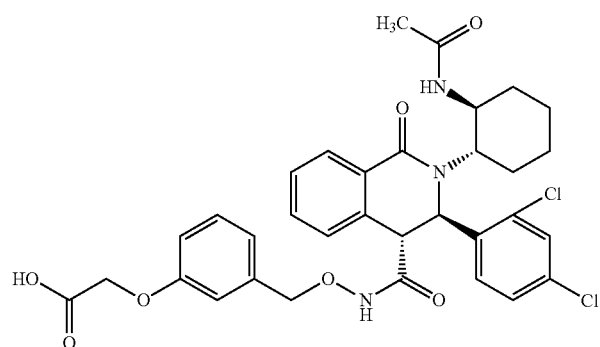
TABLE 204



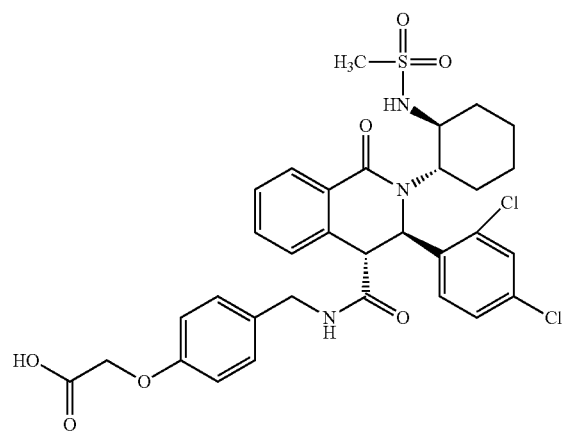
628

racemic
mixture

629

racemic
mixture

630

racemic
mixture

631

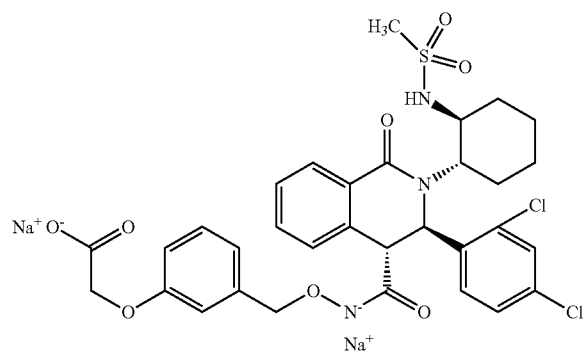


TABLE 206

632

racemic mixture

633

racemic mixture

19

racemic mixture

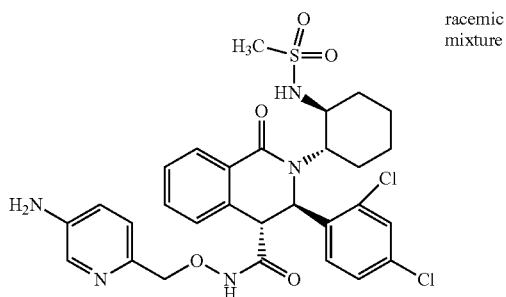
634

racemic mixture

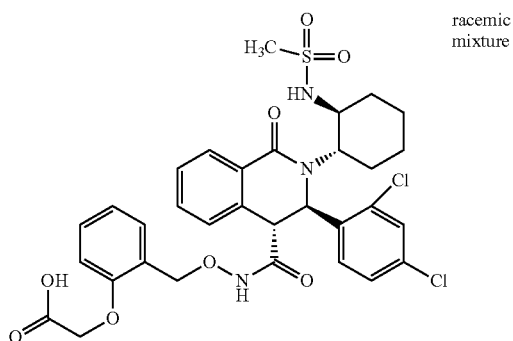
281

TABLE 207

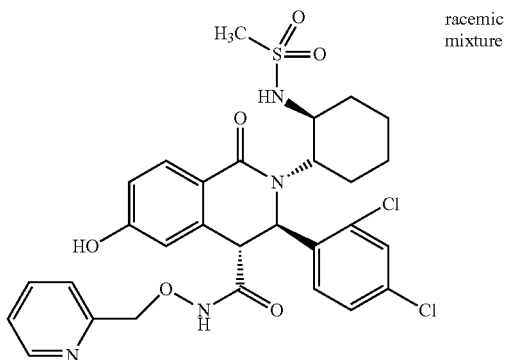
635



636



25



637

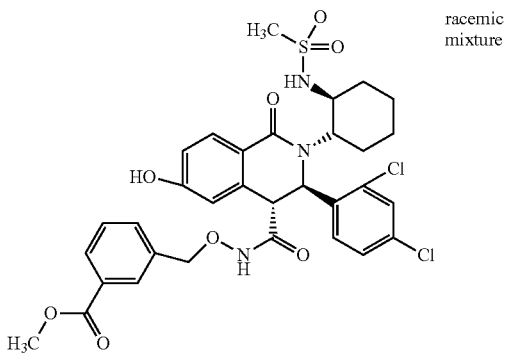
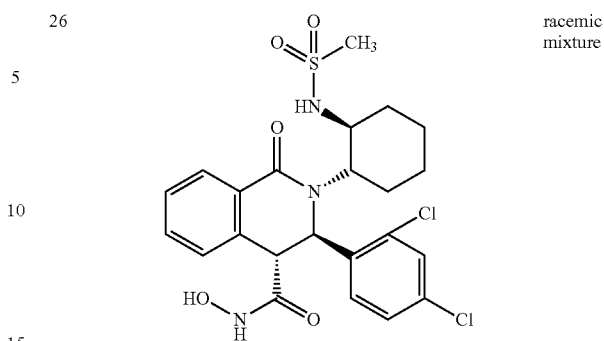
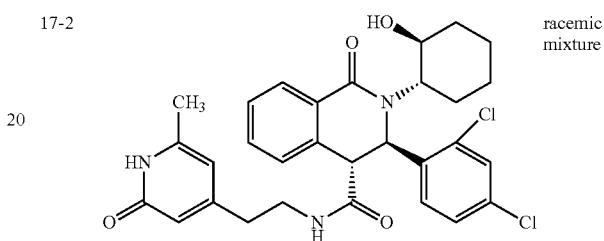
**282**

TABLE 208

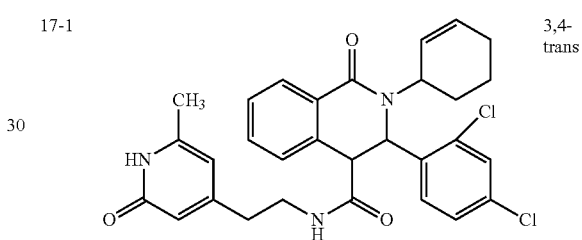
26



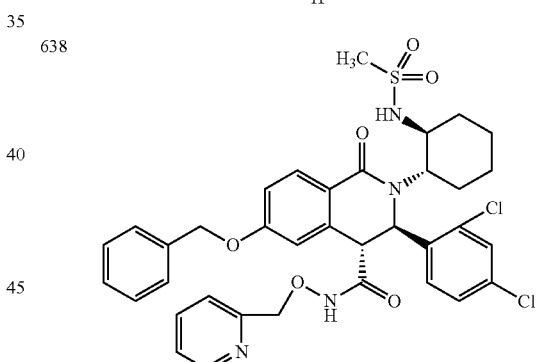
17-2



17-1



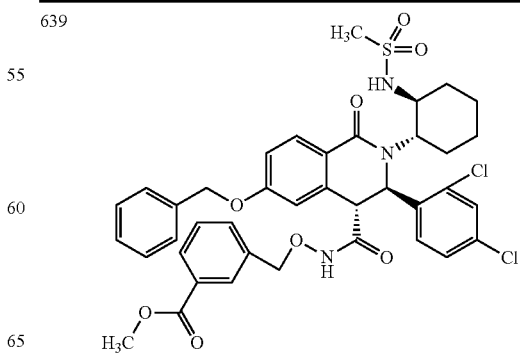
35



50

TABLE 209

639

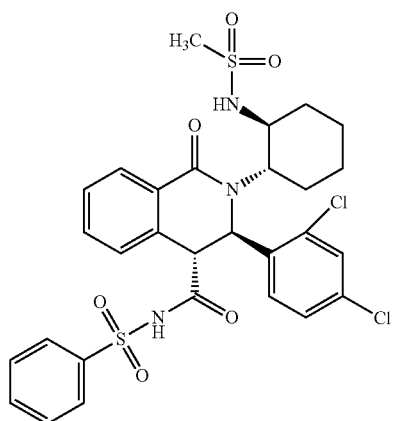


65

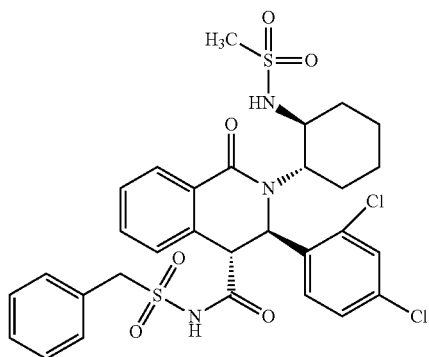
283

TABLE 209-continued

640

racemic
mixture

53

racemic
mixture

641

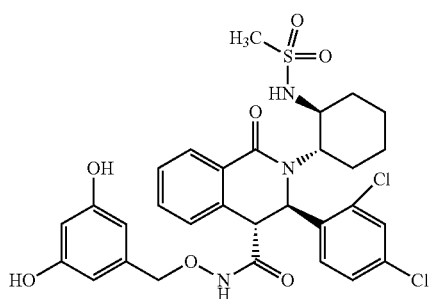
racemic
mixture**284**

TABLE 210

642

5

10

15

20

25

45

30

35

40

45

50

643

55

60

65

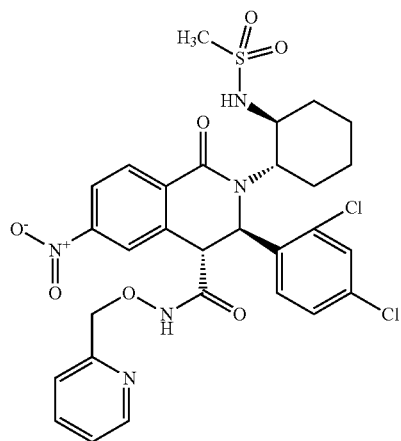
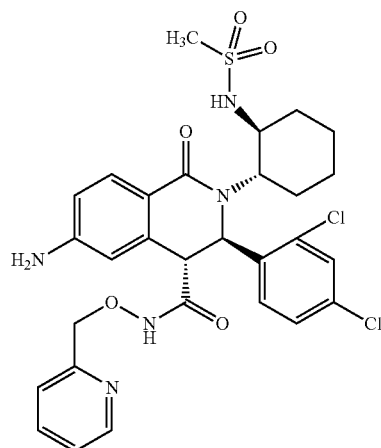
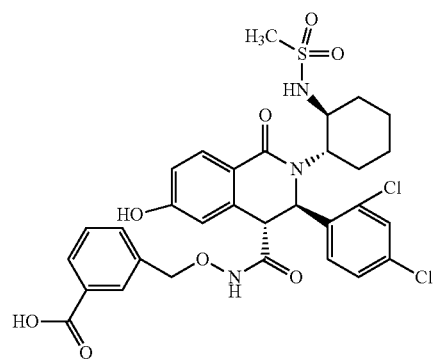
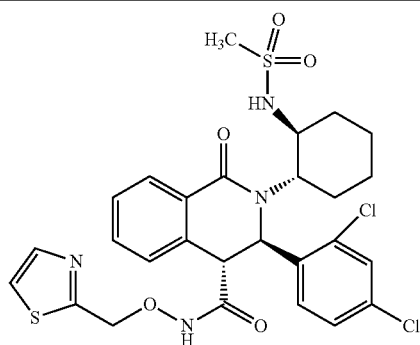
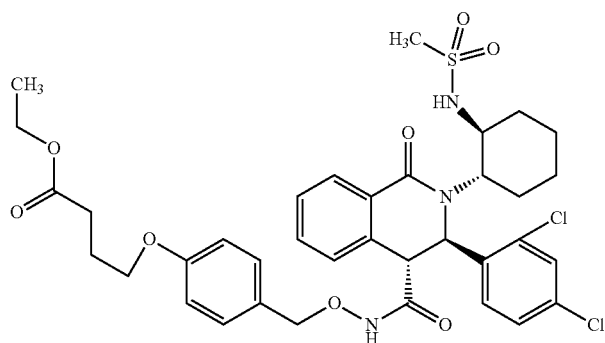
racemic
mixtureracemic
mixtureracemic
mixture

TABLE 211

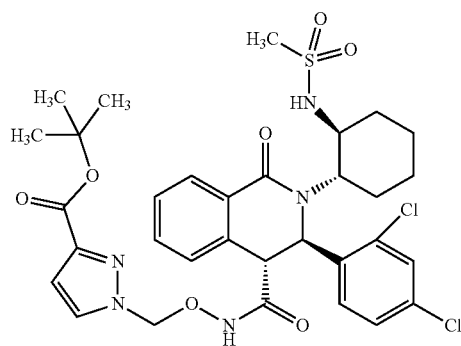
644

racemic
mixture

645

racemic
mixture

646

racemic
mixture

647

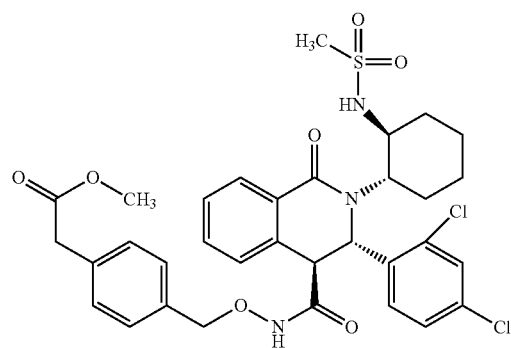
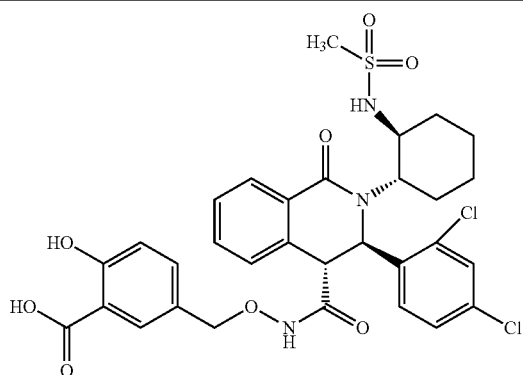
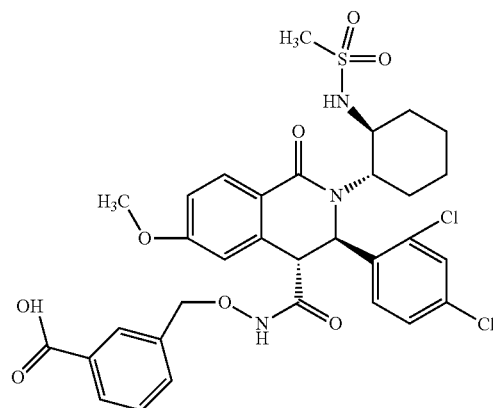


TABLE 212

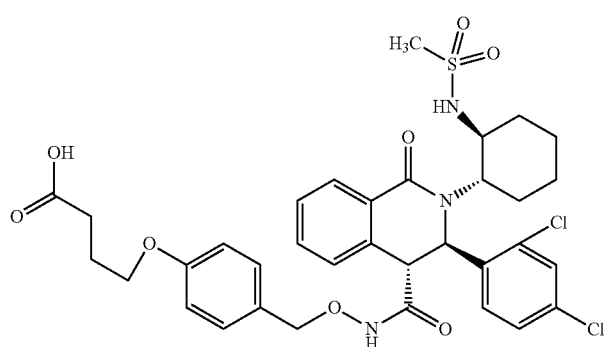
648



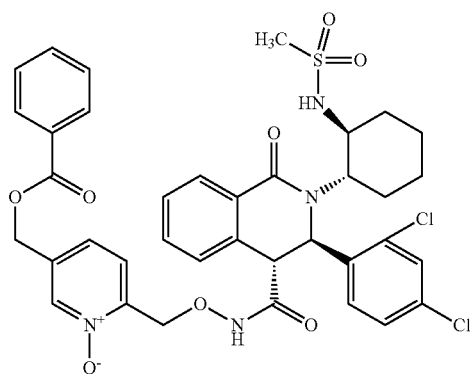
649



650

racemic
mixture

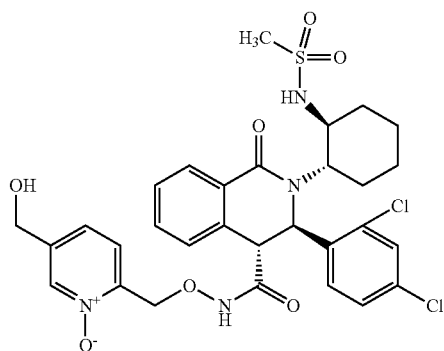
651

racemic
mixture

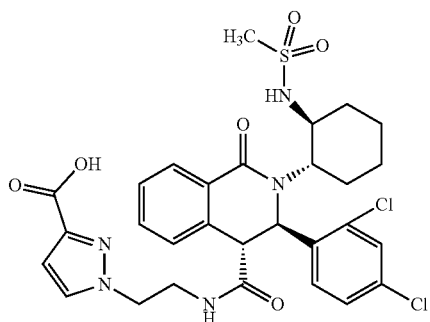
289

TABLE 213

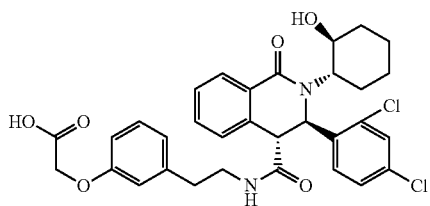
52

racemic
mixture

652

racemic
mixture

653

racemic
mixture

654

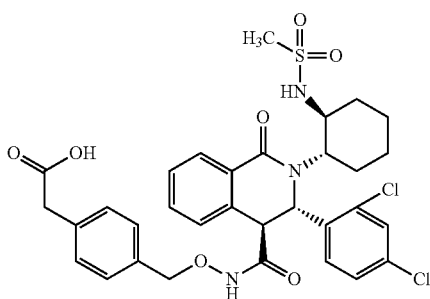
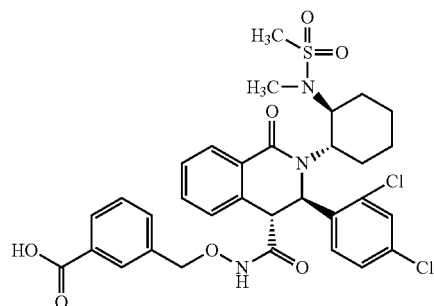
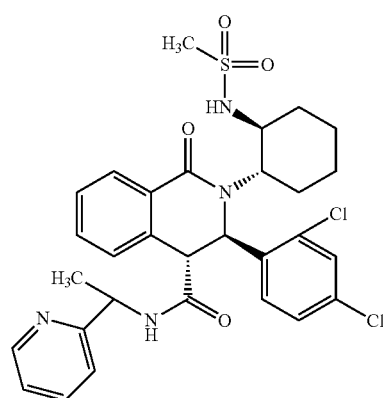
**290**

TABLE 214

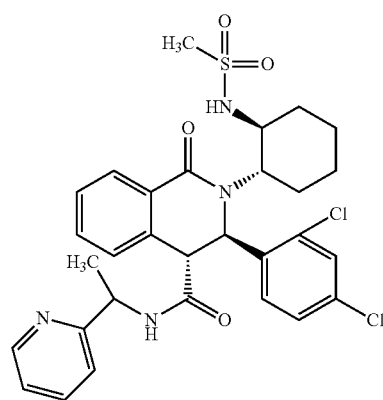
655



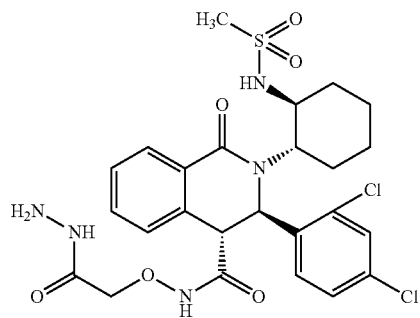
656

chiral
compound,
diaster-
eomer
of Ex 657,
more polar

657

chiral
compound,
diaster-
eomer
of Ex 656,
less polar

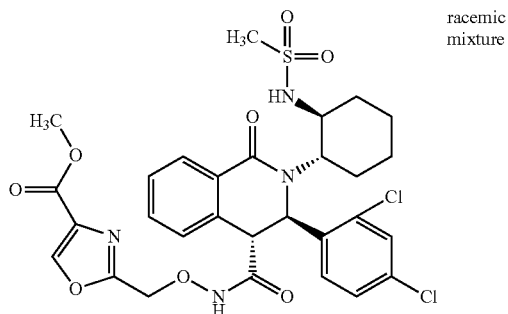
51

racemic
mixture

291

TABLE 215

658



659

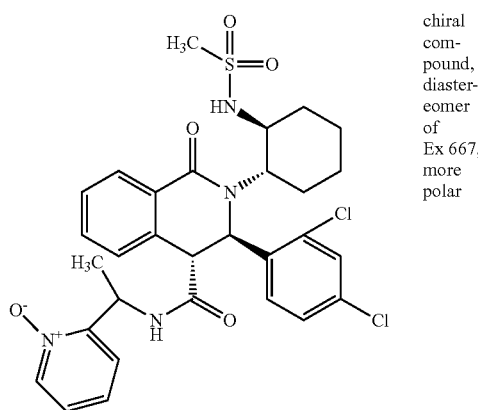
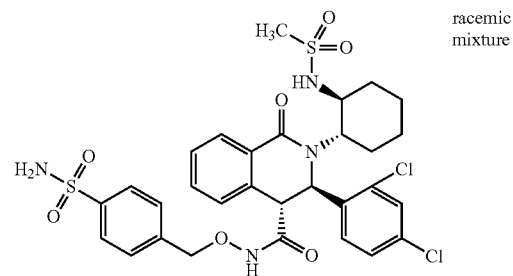
**292**

TABLE 215-continued

660

5



10

15

661

20

25

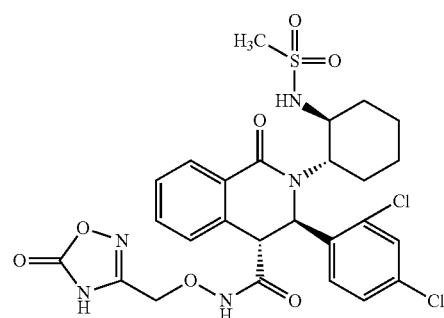
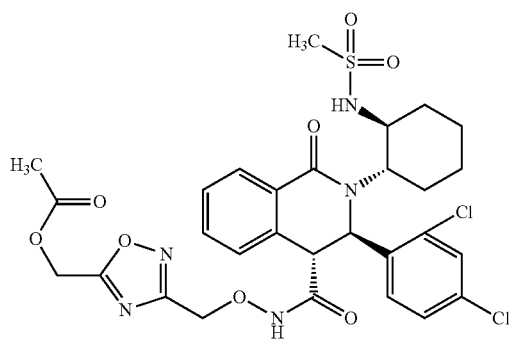
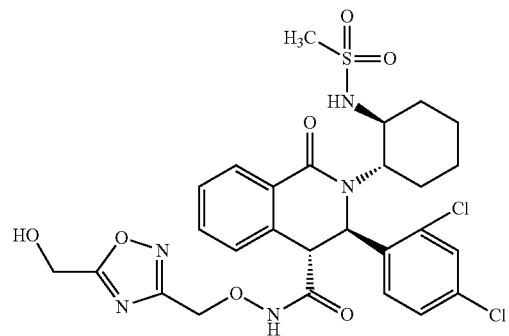


TABLE 216

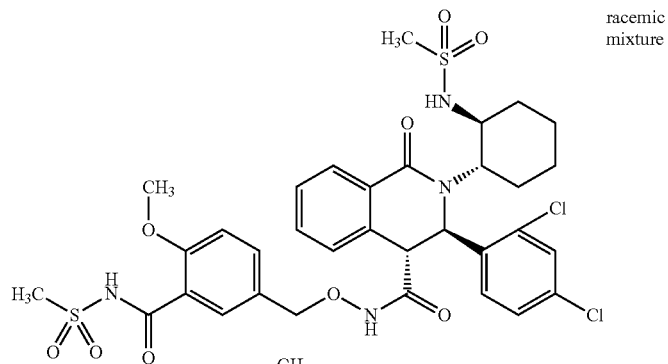
662



663



664



665

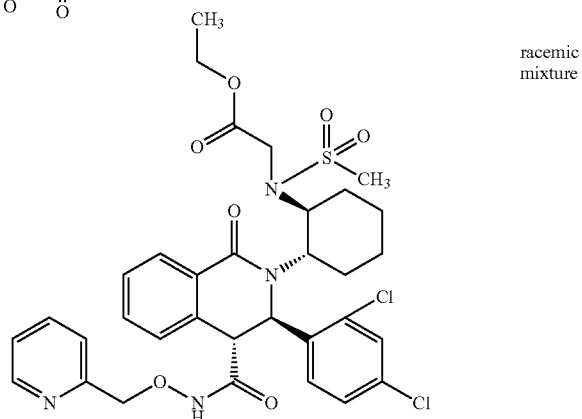
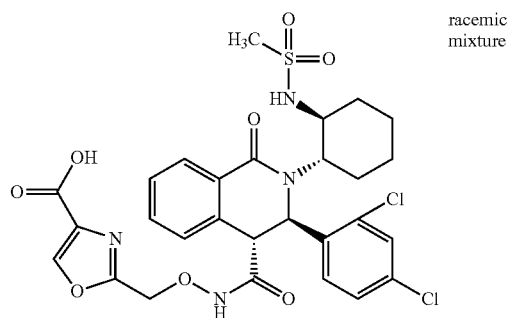


TABLE 217

666



667

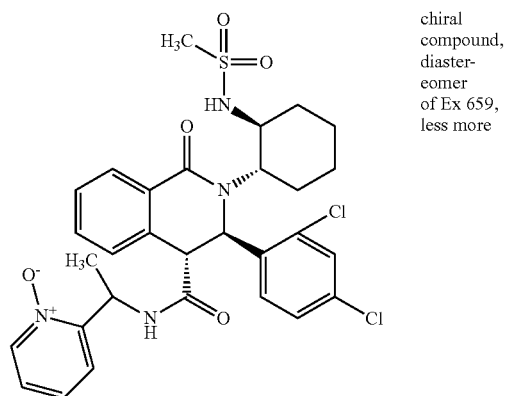
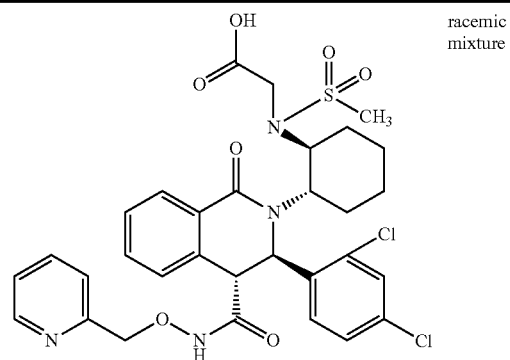
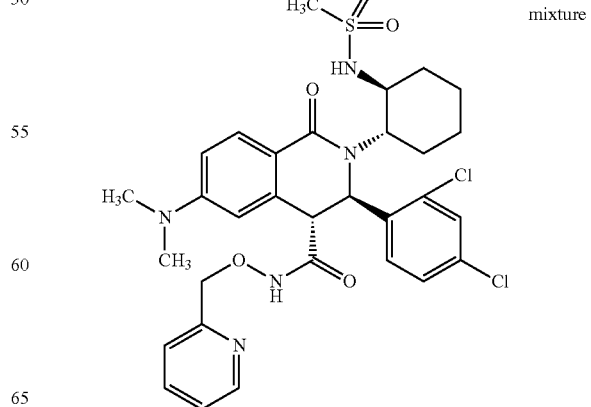


TABLE 217-continued

35
668

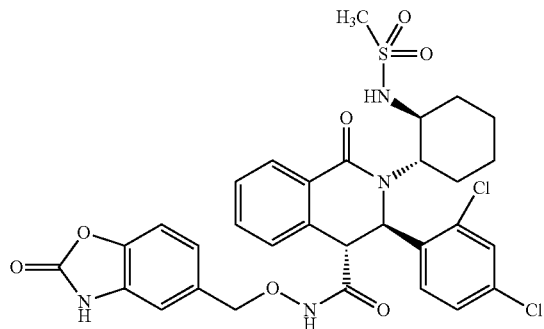
50 46



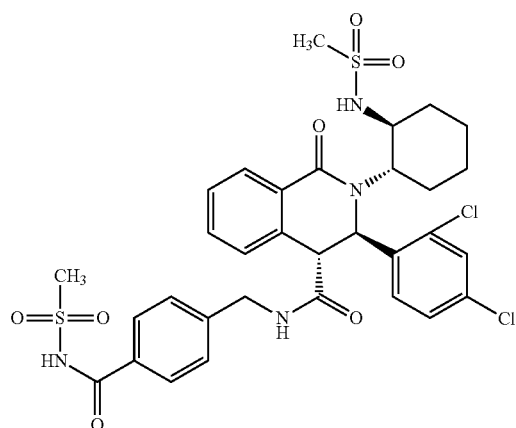
65

TABLE 218

669



670



47

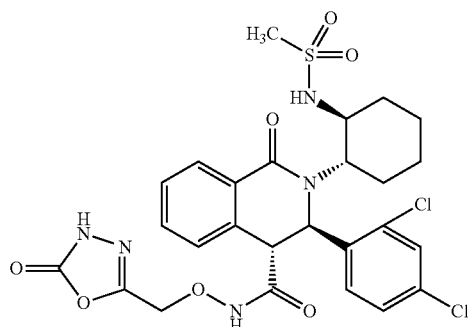


TABLE 219

671

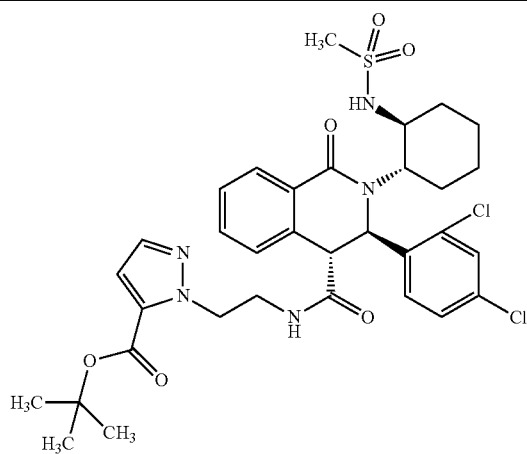


TABLE 219-continued

672



673



TABLE 220

674

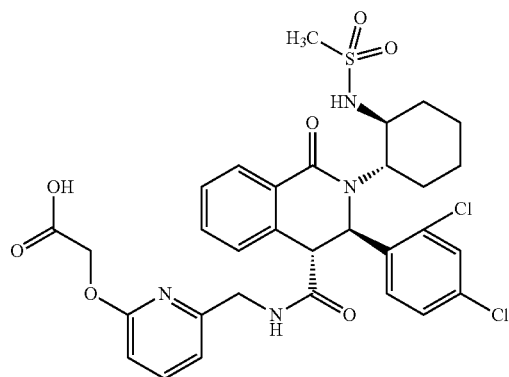


675



TABLE 220-continued

676

racemic
mixture

677

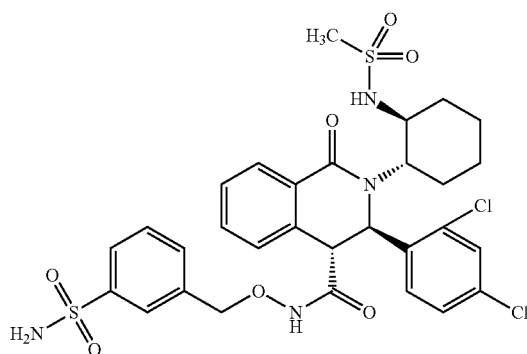
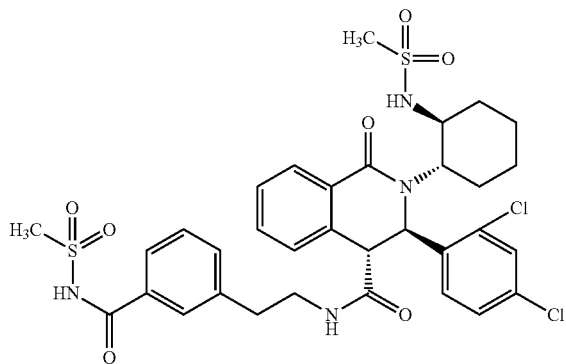
racemic
mixture

TABLE 221

678

racemic
mixture

679

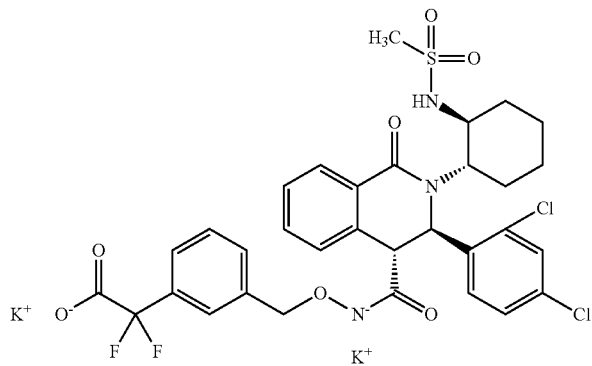
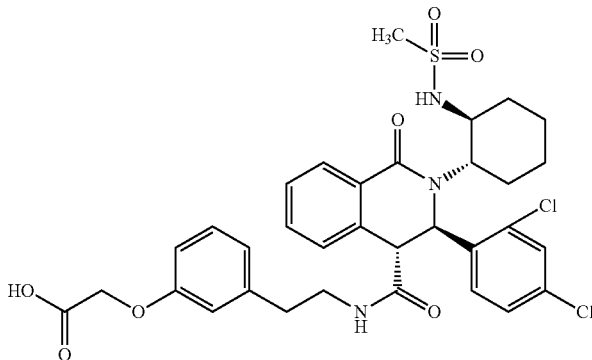


TABLE 221-continued

680



681

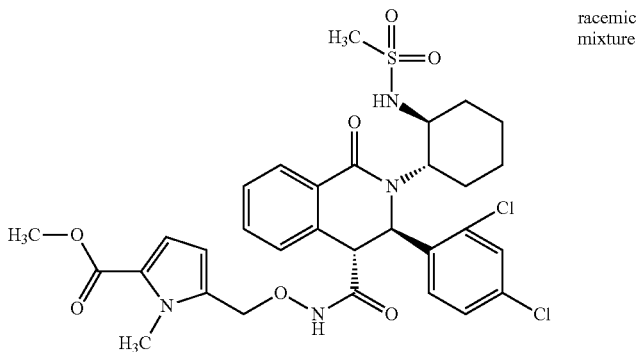
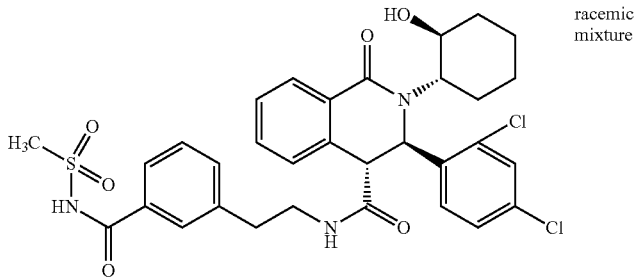


TABLE 222

682



683

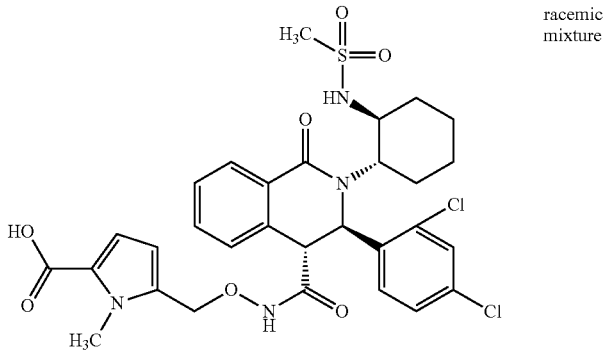
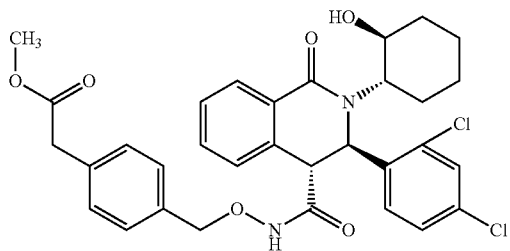


TABLE 222-continued

684

racemic
mixture

49

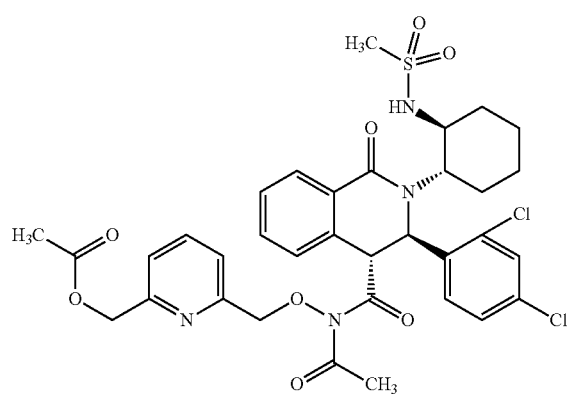
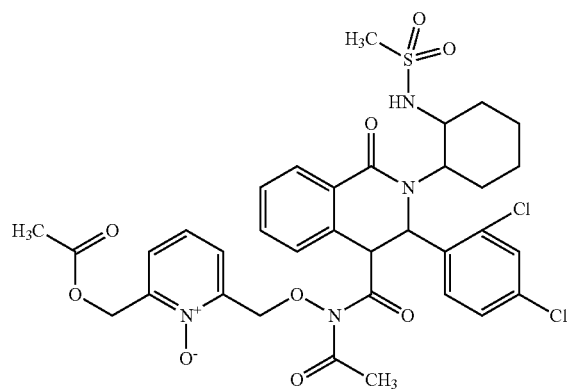
racemic
mixture

TABLE 223

685

racemic
mixture

686

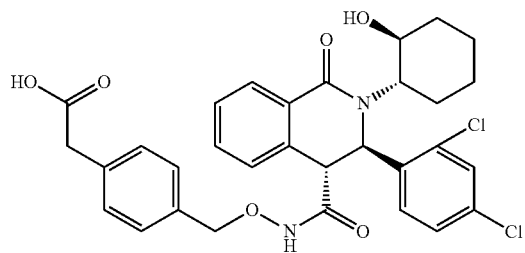
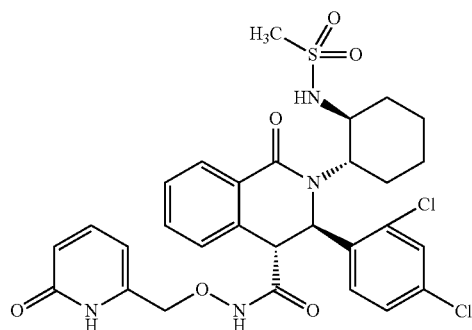
racemic
mixture

TABLE 223-continued

687

racemic
mixture

688

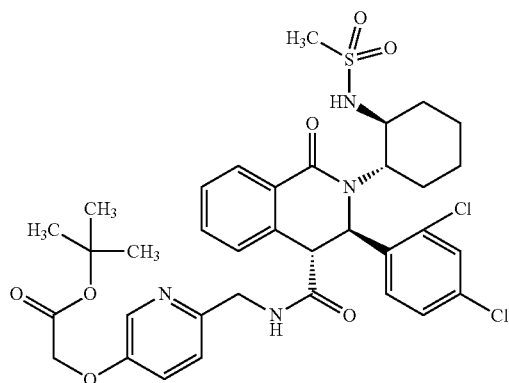
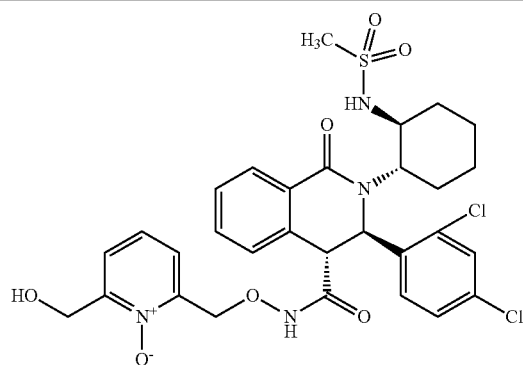
racemic
mixture

TABLE 224

55

racemic
mixture

689

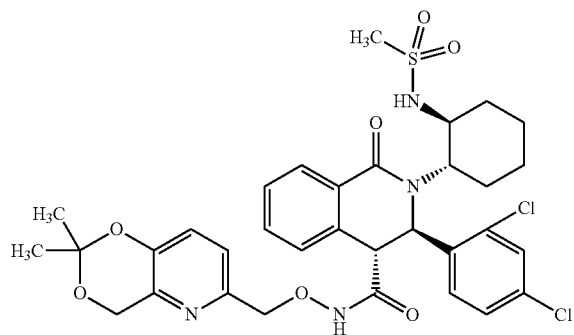
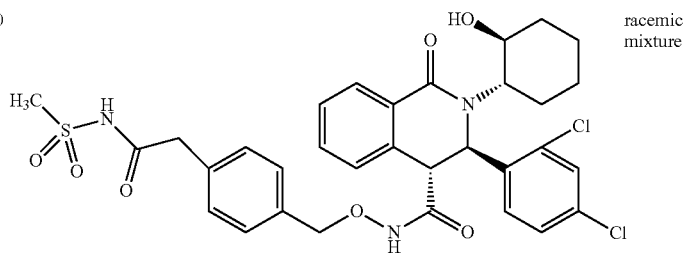
racemic
mixture

TABLE 224-continued

690



691

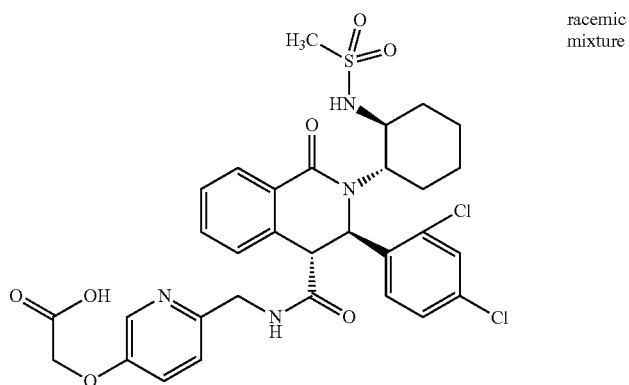
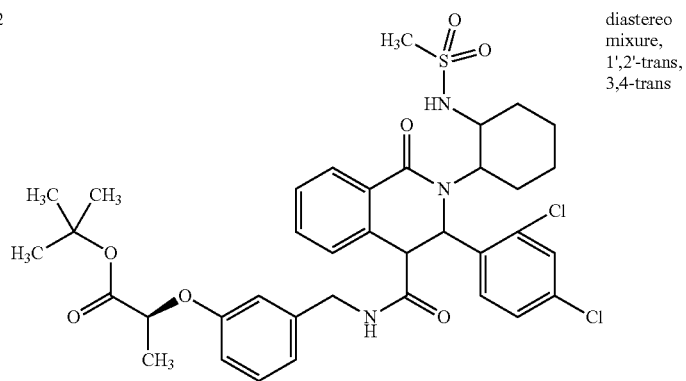


TABLE 225

692



693

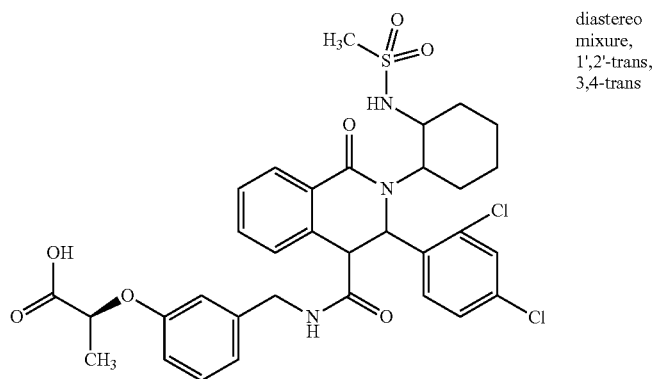
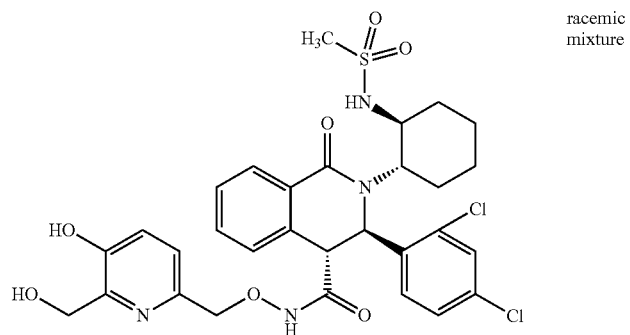


TABLE 225-continued

54



694

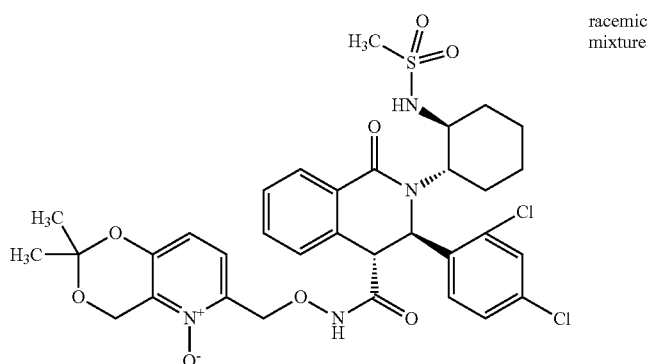
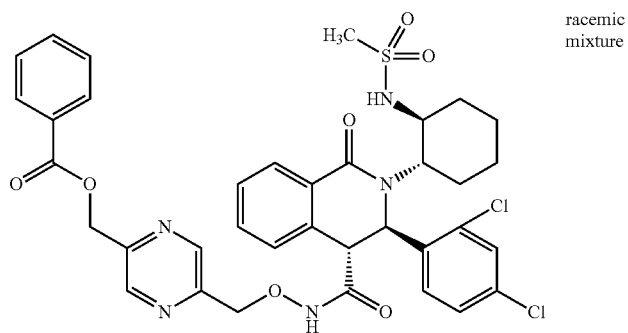


TABLE 226

695



696

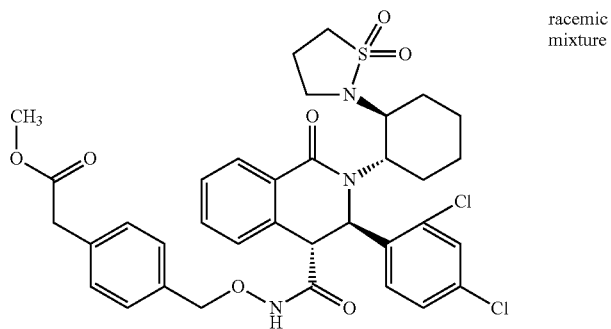
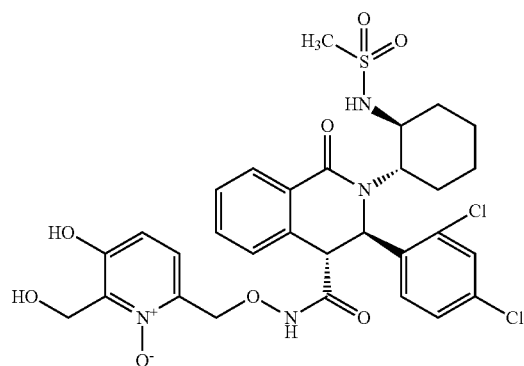


TABLE 226-continued

697

racemic
mixture

698

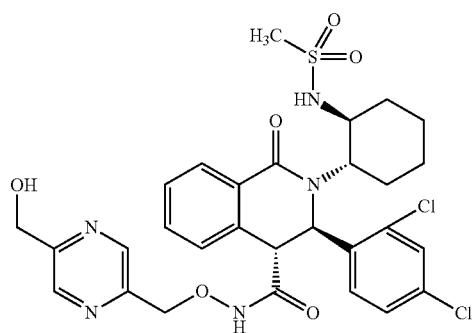
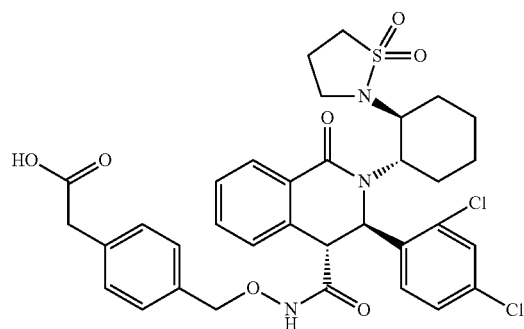


TABLE 227

699

racemic
mixture

700

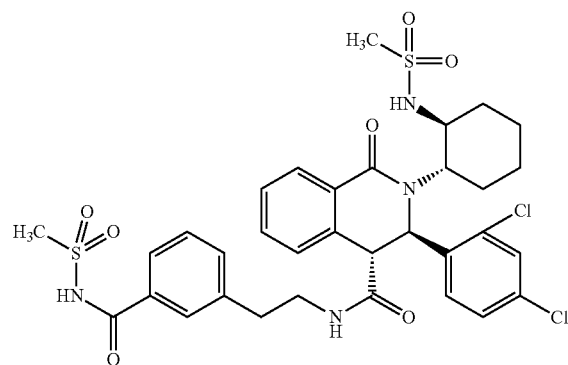
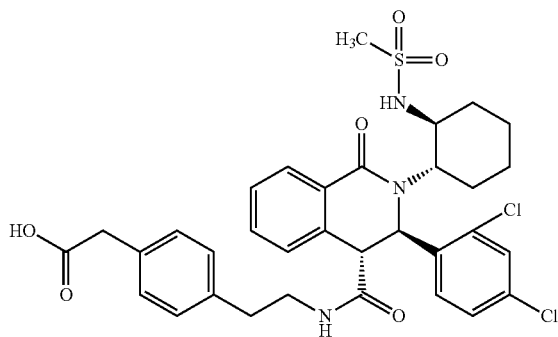
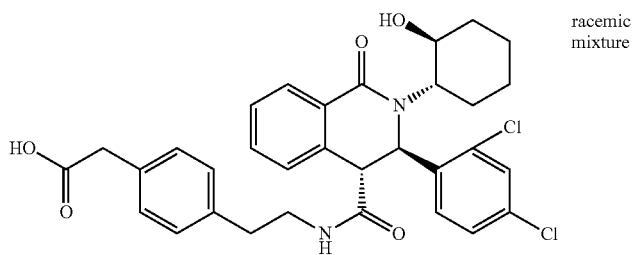


TABLE 227-continued

701



702



703

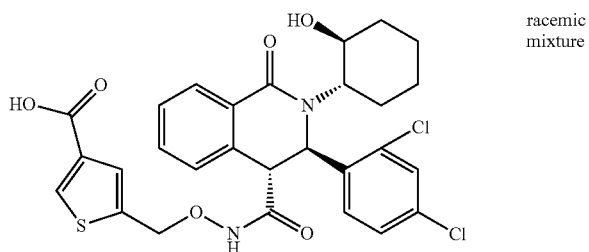
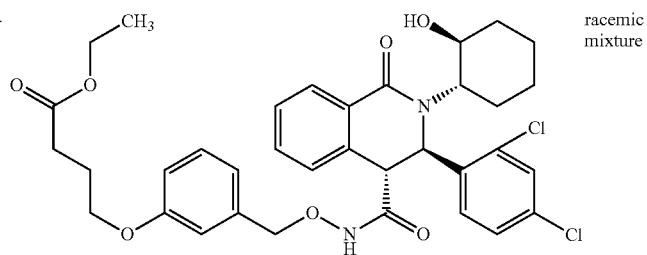


TABLE 228

704



705

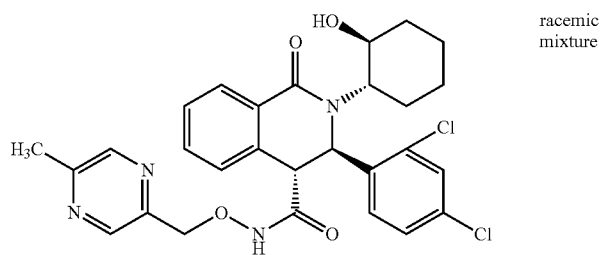
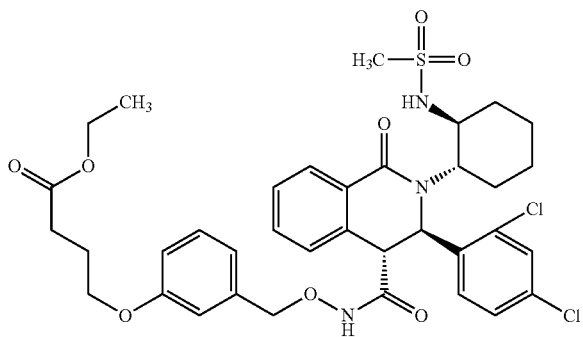
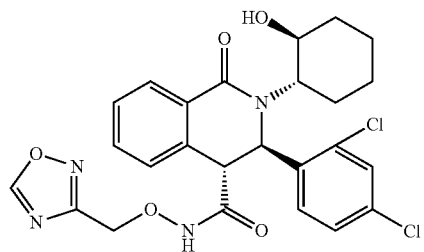


TABLE 228-continued

706



707

racemic
mixture

708

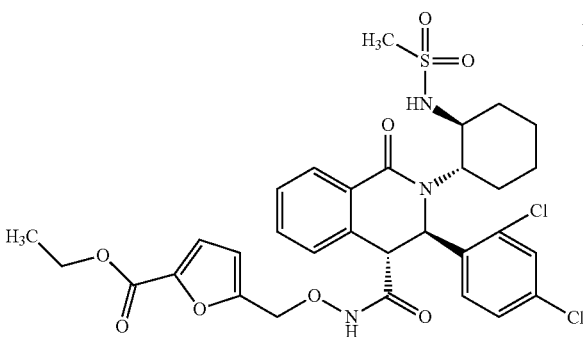
racemic
mixture

TABLE 229

44

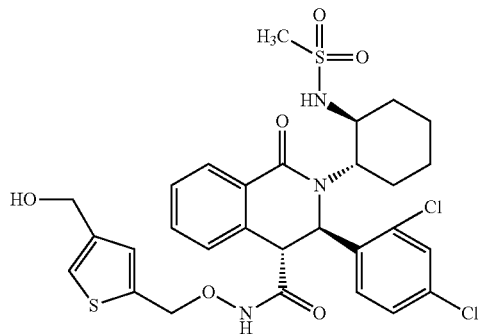
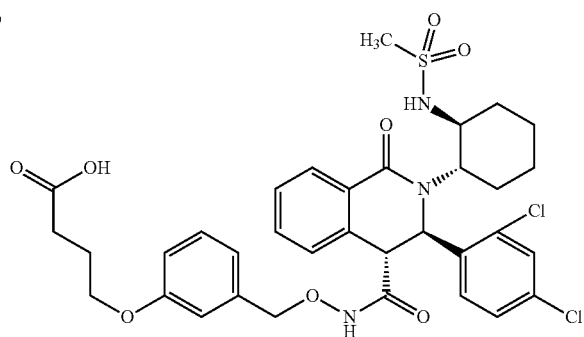
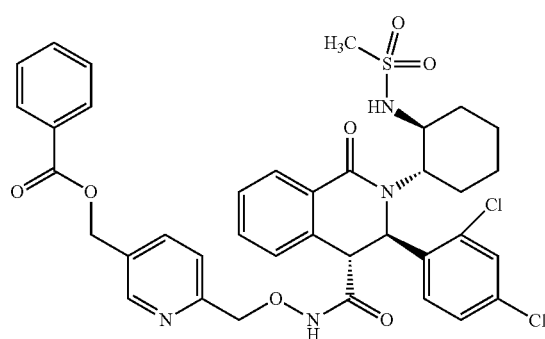
racemic
mixture

TABLE 229-continued

709



710



711

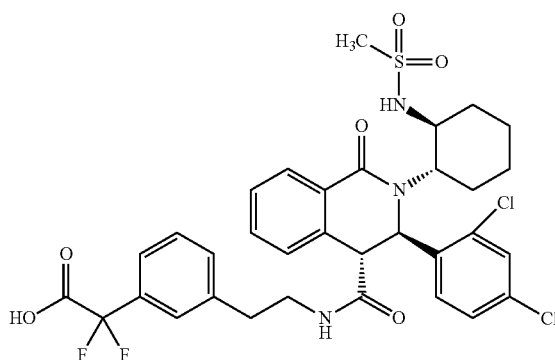


TABLE 230

712

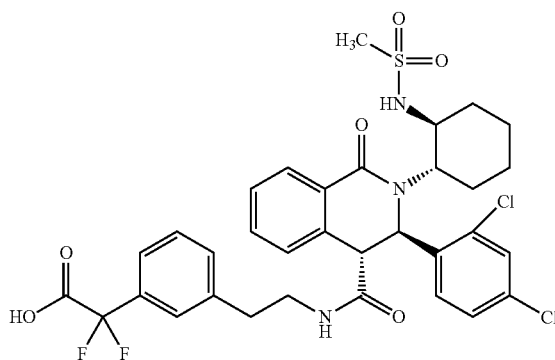
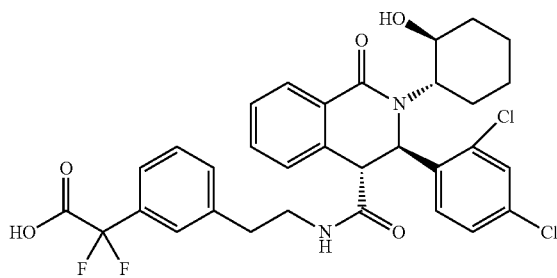


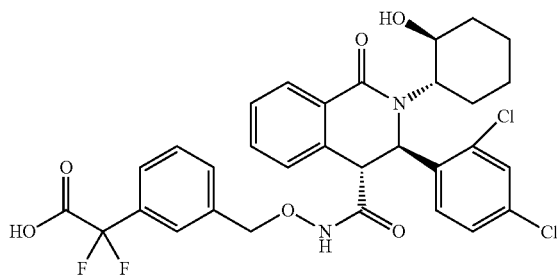
TABLE 230-continued

713

racemic
mixture

714

racemic
mixture



715

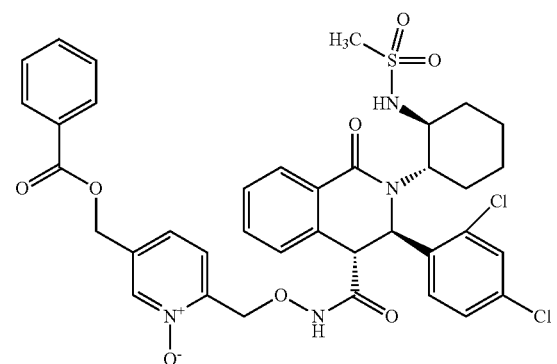


TABLE 231

57

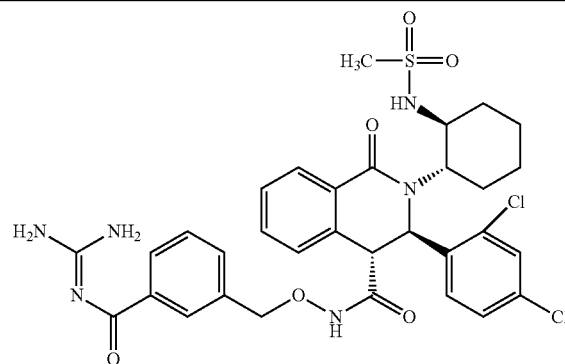
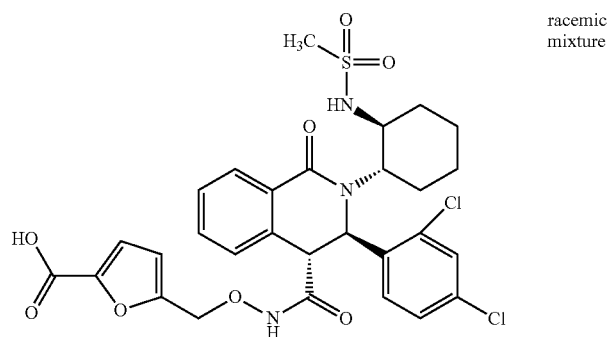
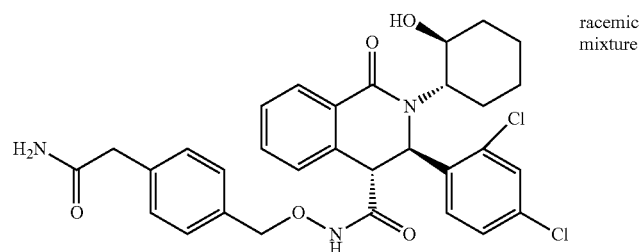
racemic
mixture

TABLE 231-continued

716



717



718

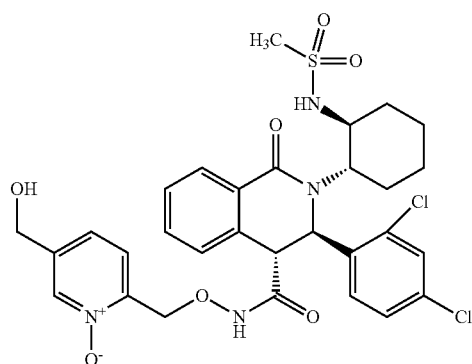


TABLE 232

719

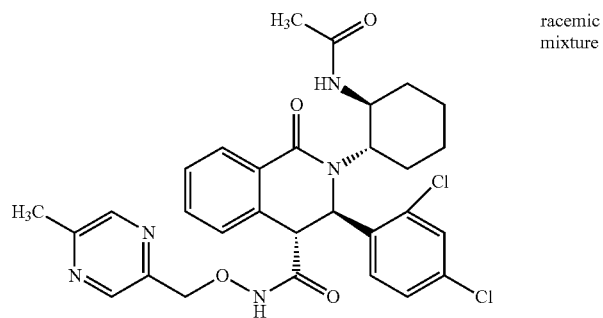
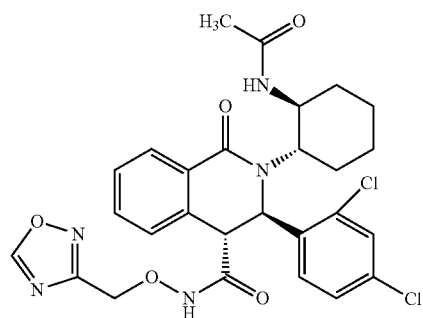
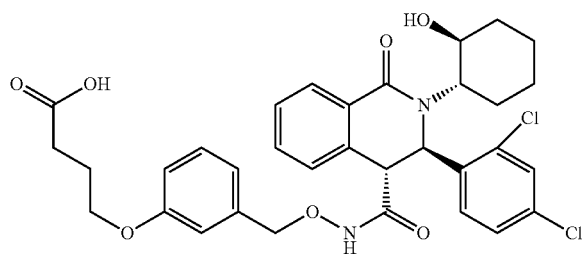


TABLE 232-continued

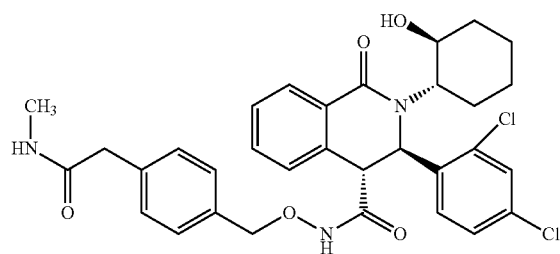
720

racemic
mixture

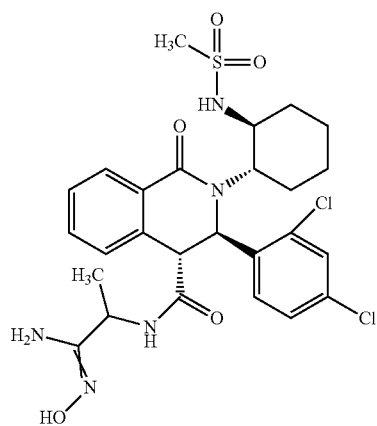
721



722



723

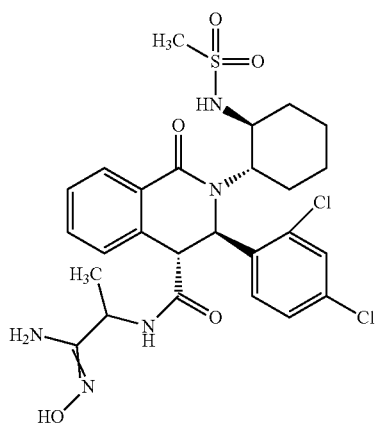
chiral
compound,
diastereomer
of Ex724,
more polar

325

TABLE 233

m

724

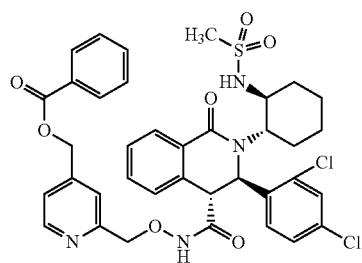
chiral
compound,
diastereomer
of Ex723,
less polar

326

TABLE 233-continued

725

5

racemic
mixture

10

726

15

20

25

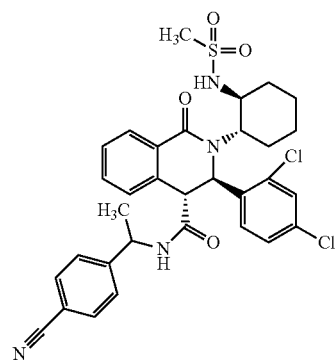
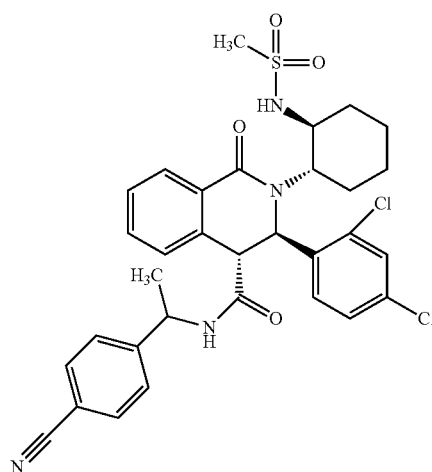
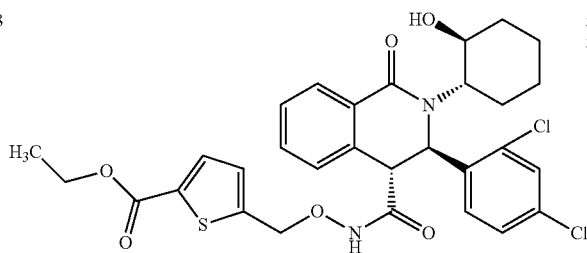
chiral
compound,
diastereomer
of Ex727,
less polar

TABLE 234

724

chiral
compound,
diastereomer
of Ex726,
more polar

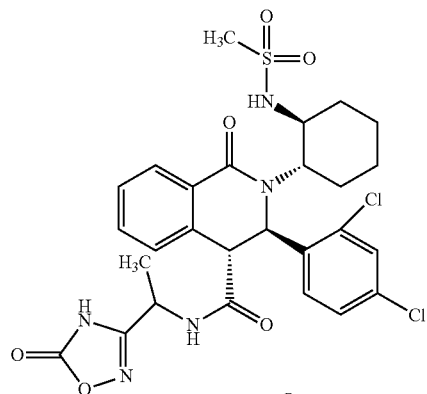
728

racemic
mixture

327

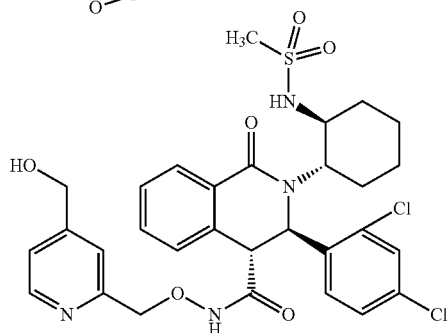
TABLE 234-continued

729



chiral
compound,
diastereomer
of Ex733,
more polar

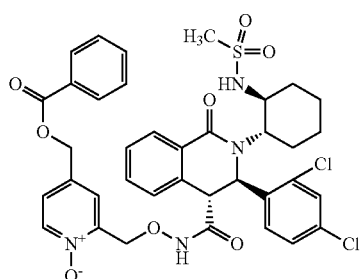
730



racemic
mixture

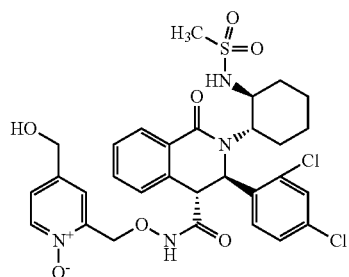
TABLE 235

731



racemic
mixture

732

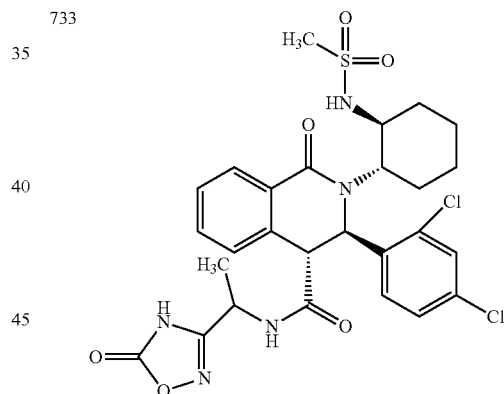


racemic
mixture

328

TABLE 235-continued

733

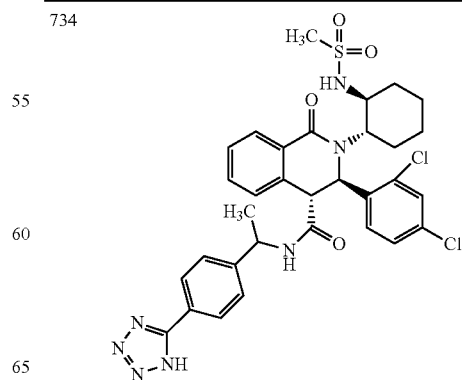


chiral
compound,
diastereomer
of Ex729,
less polar

50

TABLE 236

734



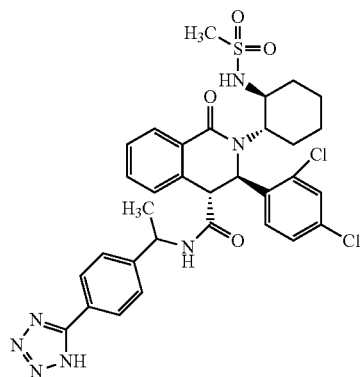
chiral
compound,
diastereomer
of Ex735,
more polar

65

329

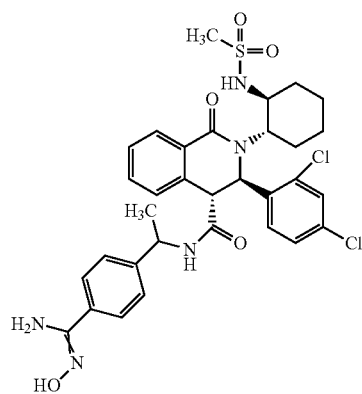
TABLE 236-continued

735



chiral
compound,
diastereomer
of Ex734,
less polar

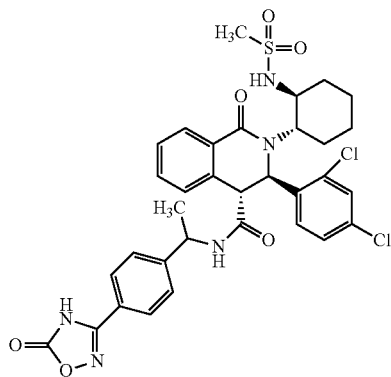
736



chiral
compound,
diastereomer
of Ex738,
more polar

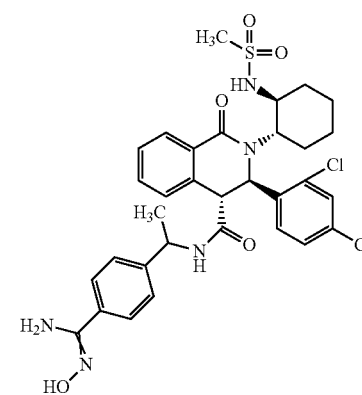
TABLE 237

737



chiral
compound

738



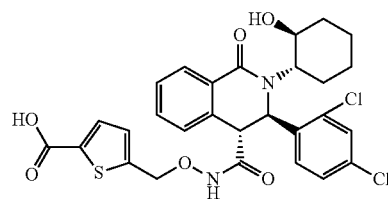
chiral
compound,
diastereomer
of Ex736,
less polar

330

TABLE 237-continued

739

5

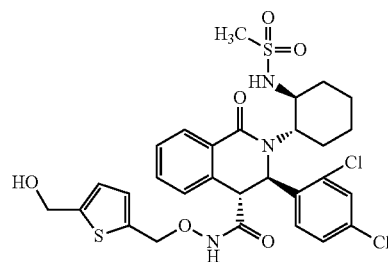


racemic
mixture

10

740

15



racemic
mixture

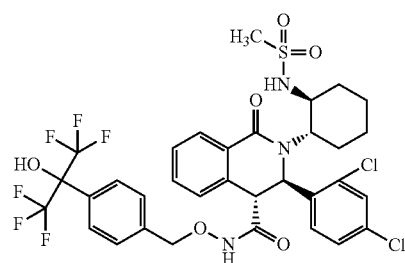
20

25

TABLE 238

741

30



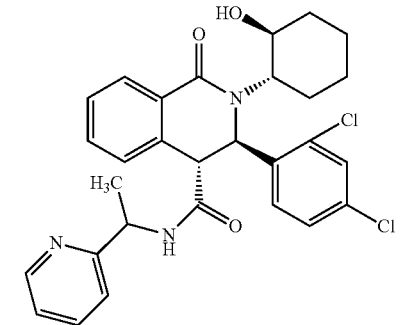
racemic
mixture

35

40

742

45

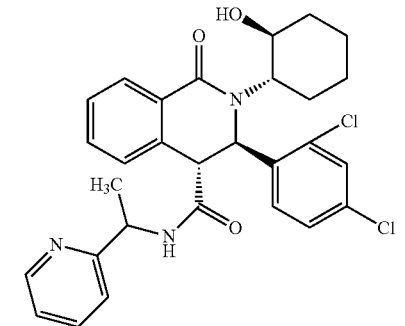


racemic
mixture,
diastereomer
of Ex743,
less polar

50

743

55



racemic
mixture,
diastereomer
of Ex742,
more polar

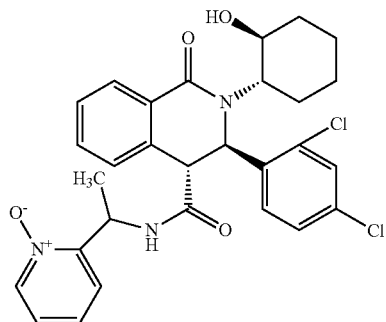
60

65

331

TABLE 238-continued

744

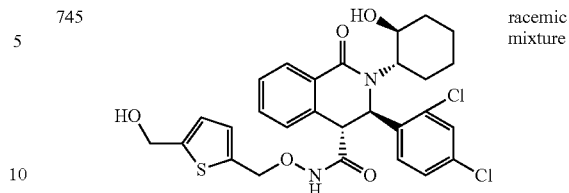


racemic
mixture,
diastereomer
of Ex749,
less polar

332

TABLE 238-continued

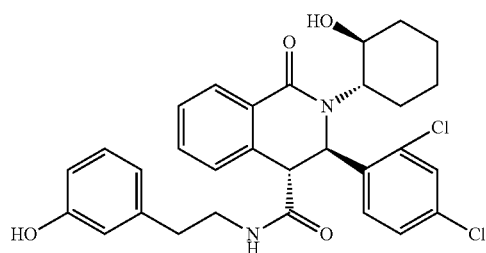
745



racemic
mixture

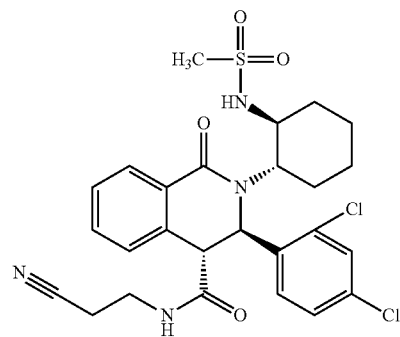
TABLE 239

746



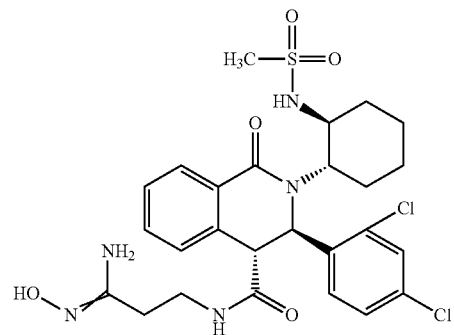
racemic
mixture

747



racemic
mixture

748



racemic
mixture

TABLE 239-continued

59

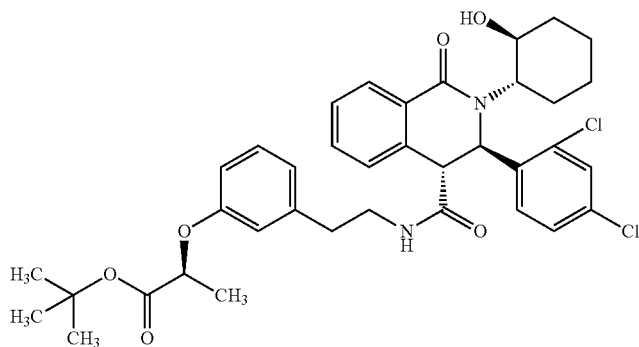
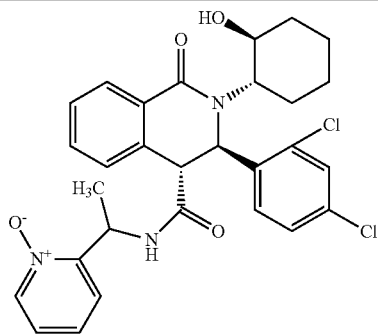


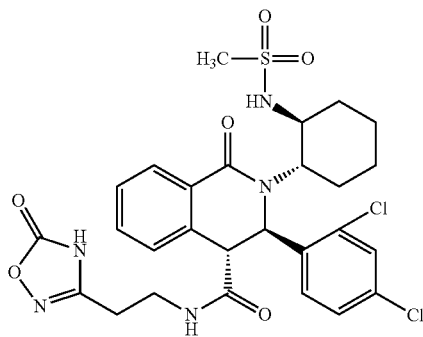
TABLE 240

749



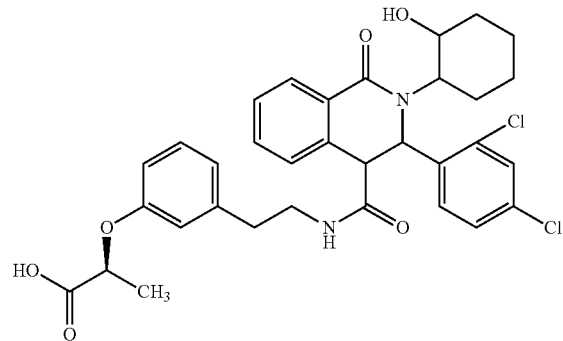
racemic
mixture,
diastereomer
of Ex744,
more polar

750



racemic
mixture

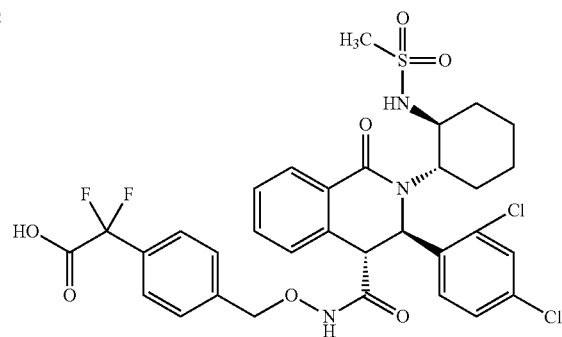
751



diastere
mixture,
1',2'-trans,
3,4-trans

TABLE 240-continued

752



753

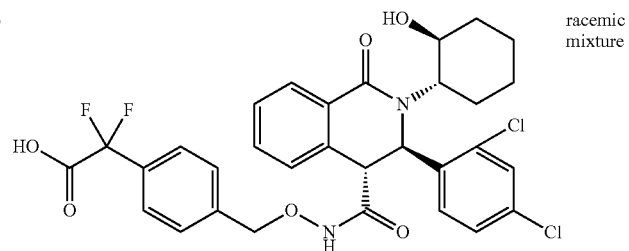
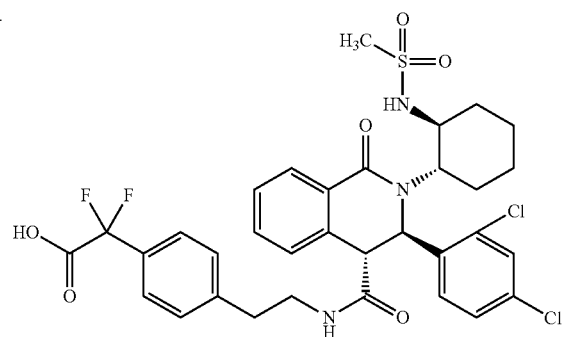
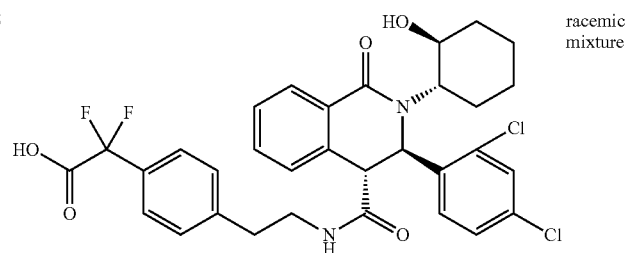


TABLE 241

754



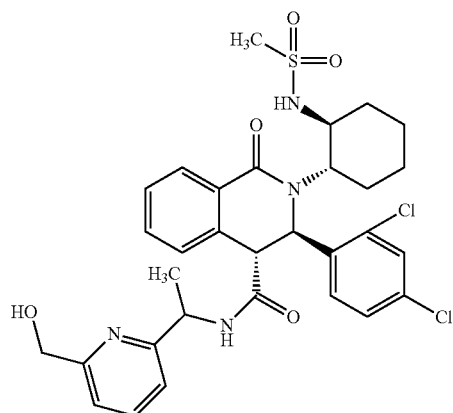
755



337

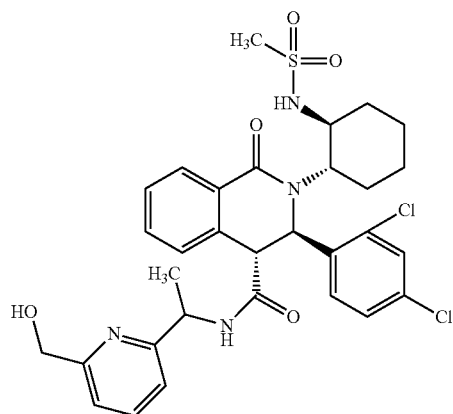
TABLE 241-continued

756



chiral
compound,
diastereomer
of Ex757,
less polar

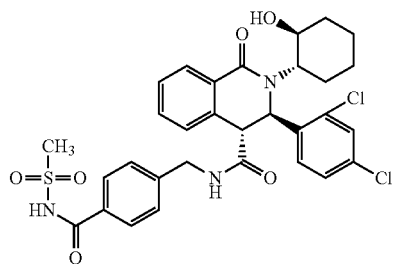
757



chiral
compound,
diastereomer
of Ex756,
more polar

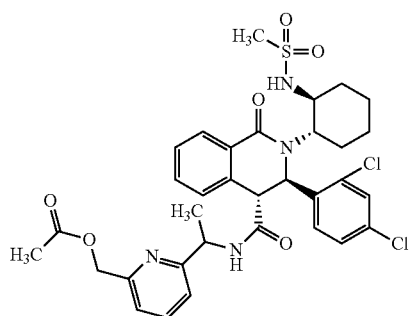
TABLE 242

758



racemic
mixture

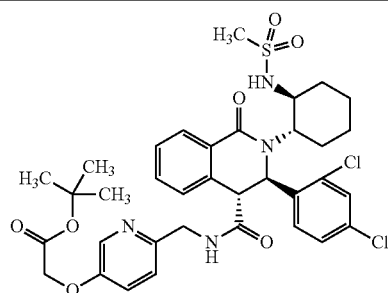
50



chiral
compound

TABLE 242-continued

759



45

50

55 760

60

65

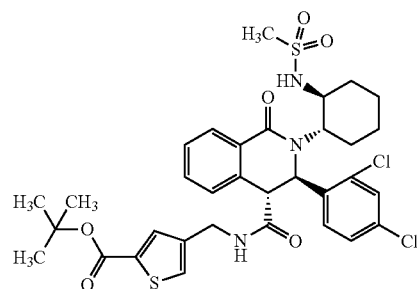
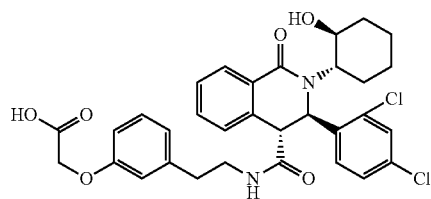
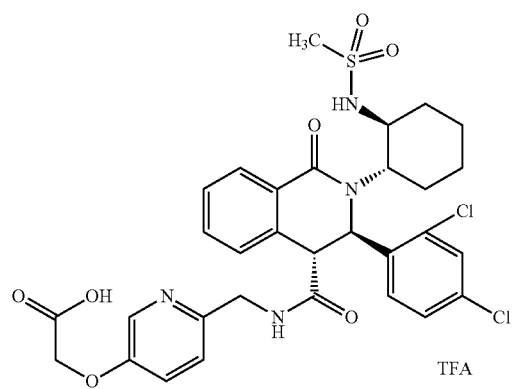


TABLE 243

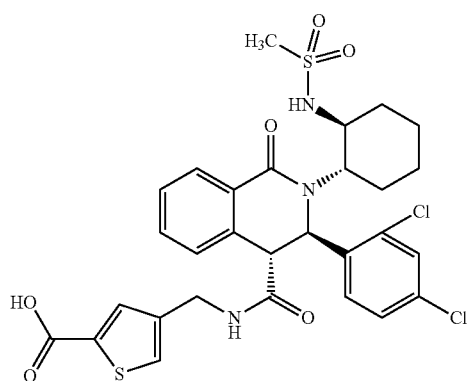
761



762



763



764

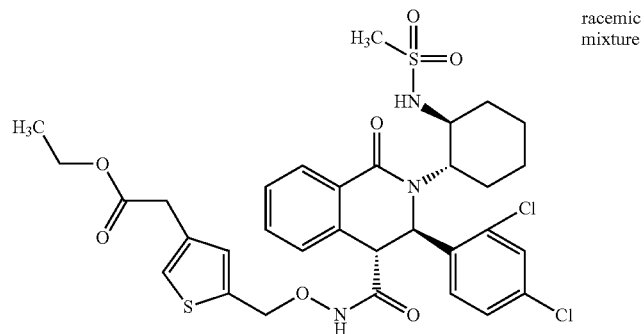
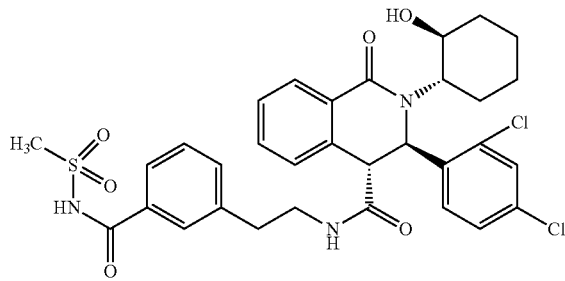
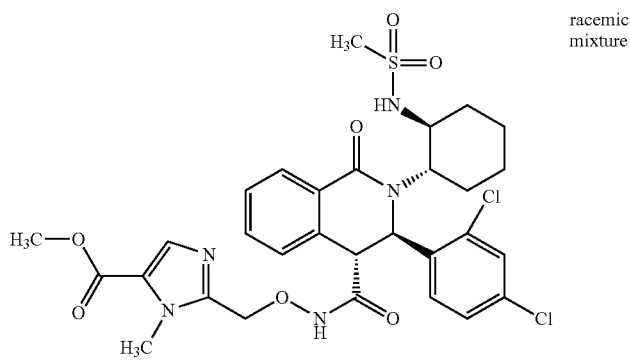


TABLE 244

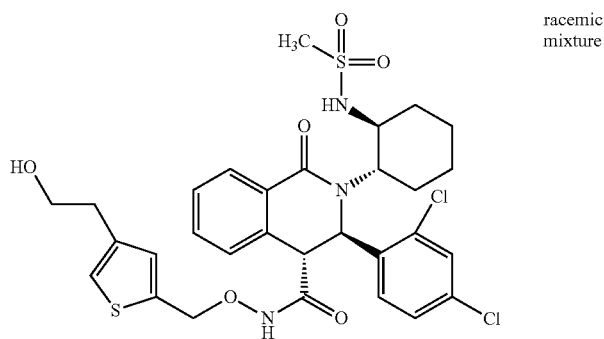
765



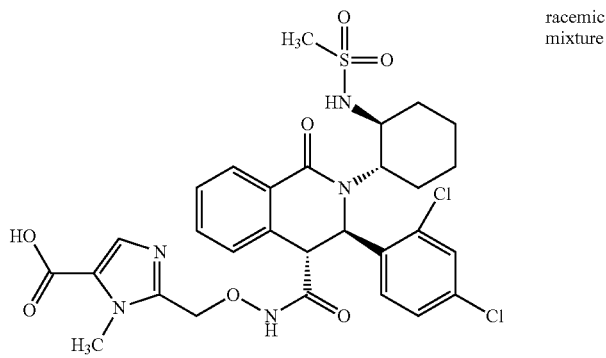
766

racemic
mixture

767

racemic
mixture

768

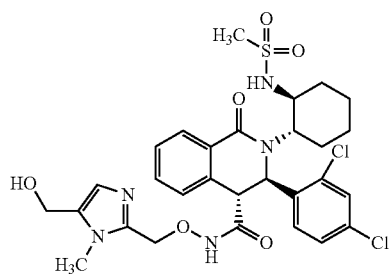


racemic
mixture

343

TABLE 245

769

racemic
mixture

770

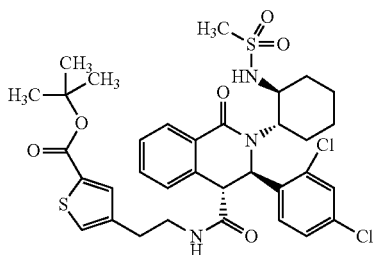
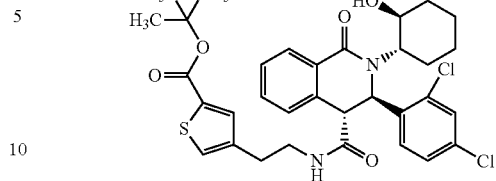
**344**

TABLE 245-continued

771

racemic
mixture

772

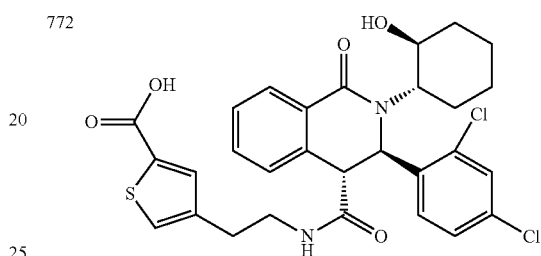
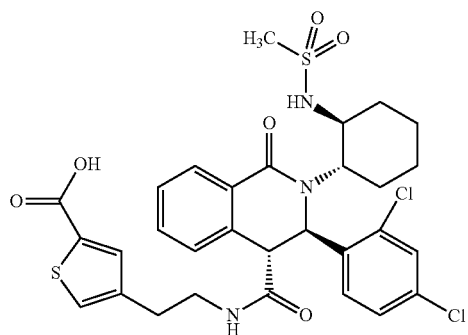
racemic
mixture

TABLE 246

773



774

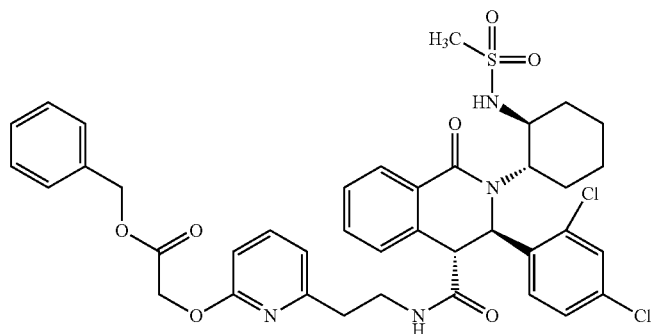
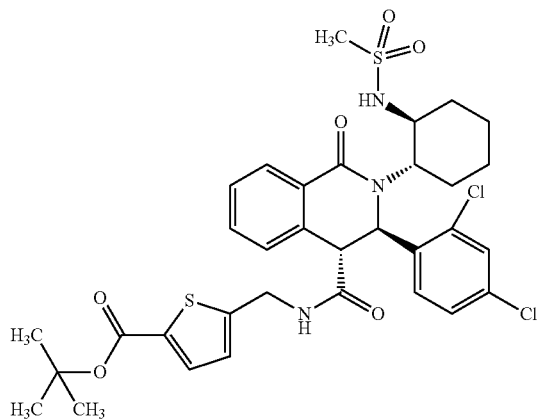
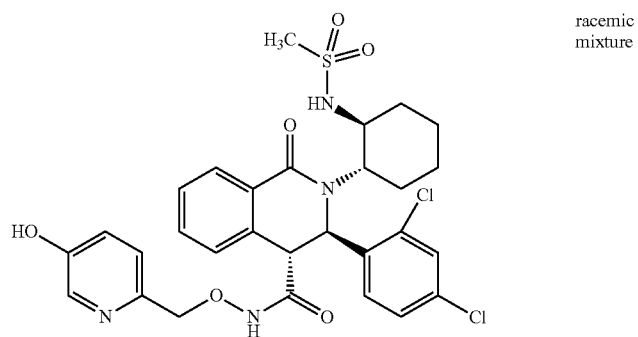
racemic
mixture

TABLE 246-continued

775



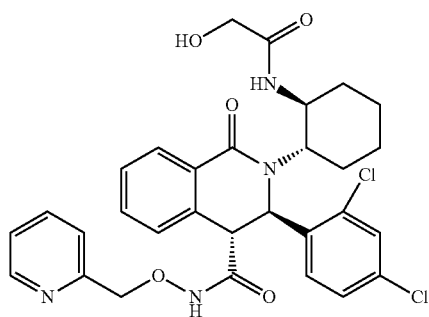
776

racemic
mixture

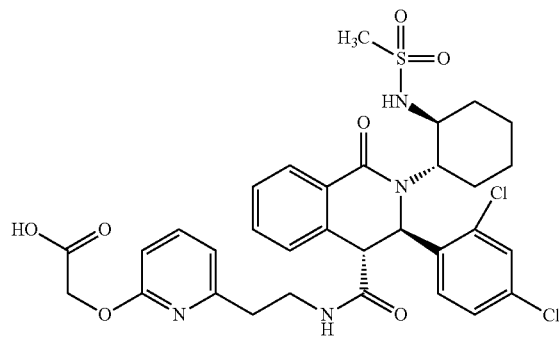
35

TABLE 247

777

racemic
mixture

48

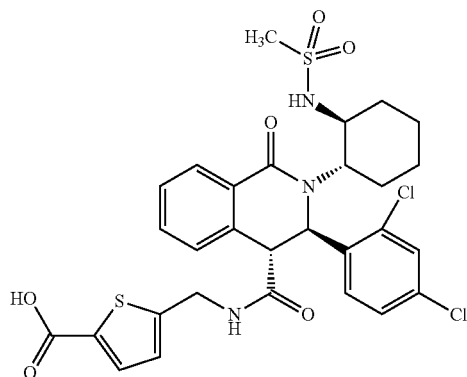
racemic
mixture

347

348

TABLE 247-continued

778



779

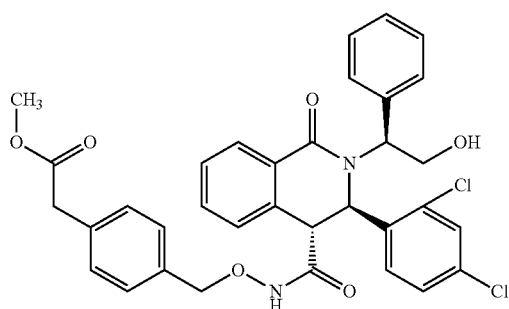
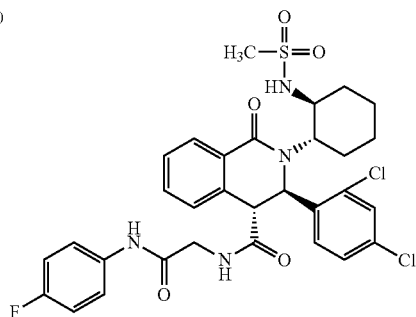
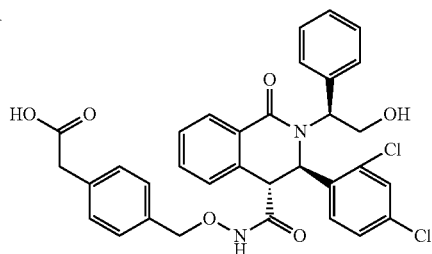


TABLE 248

780



781



782

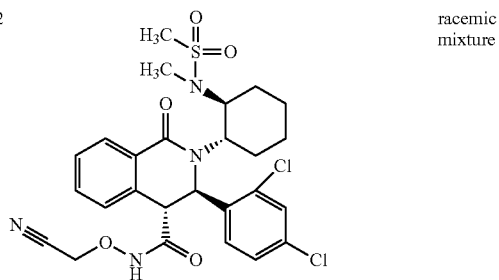
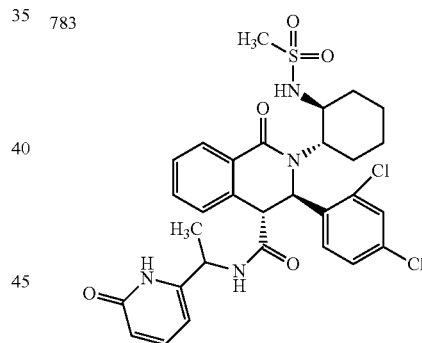


TABLE 248-continued

35 783



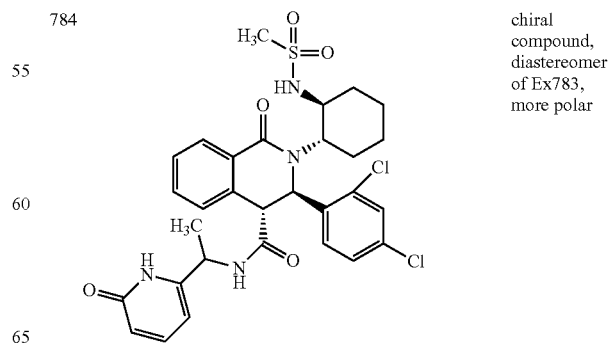
40

45

50

TABLE 249

784



55

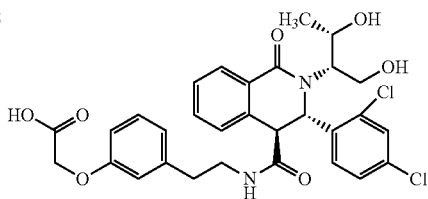
60

65

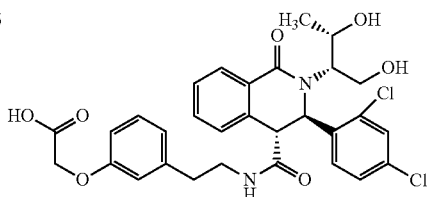
349

TABLE 249-continued

785



786



787

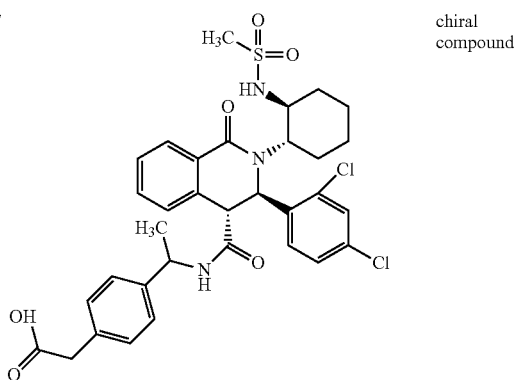
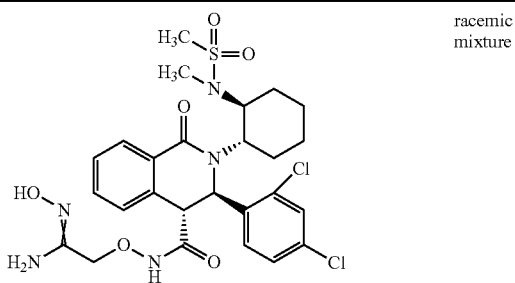


TABLE 250

788



789

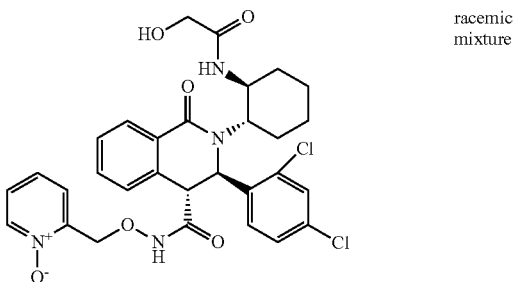
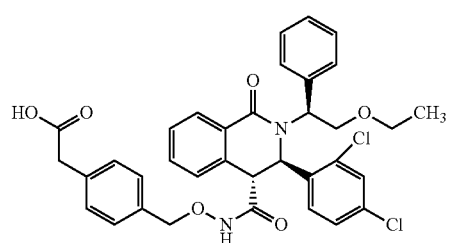
**350**

TABLE 250-continued

790

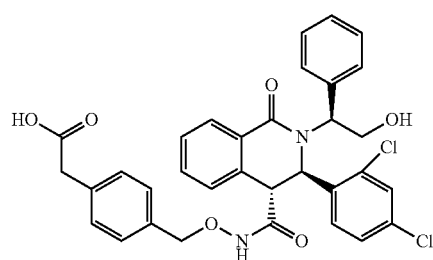
5



10

791

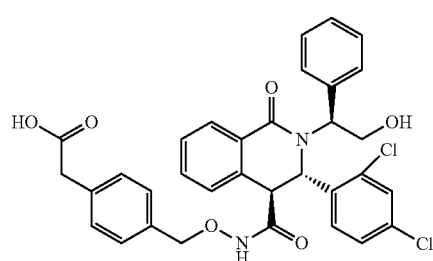
15



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25

792



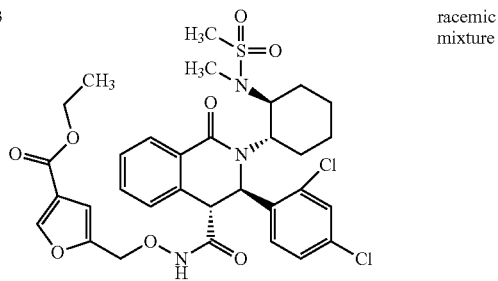
30

35

TABLE 251

40

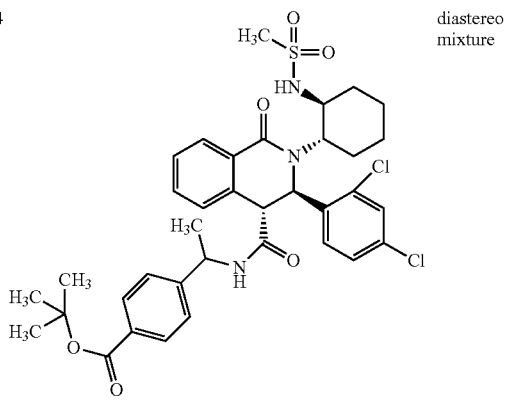
793



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794



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65

351

TABLE 251-continued

795

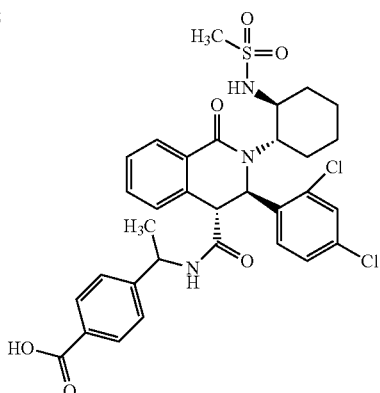
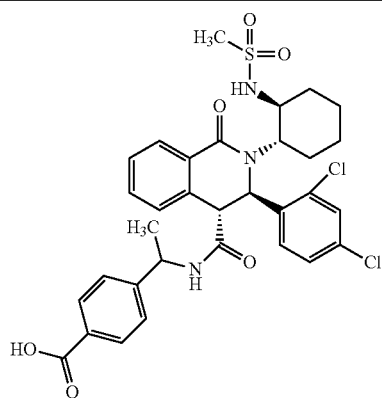
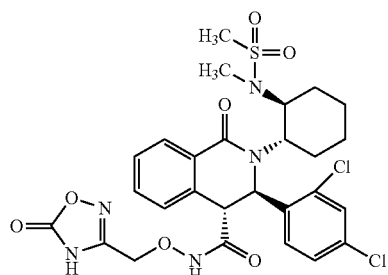


TABLE 252

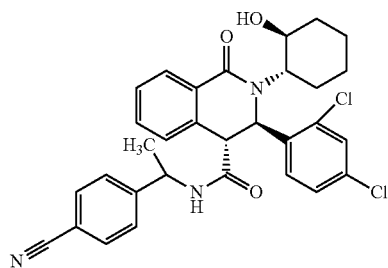
796



797



798



352

TABLE 252-continued

799

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10

15

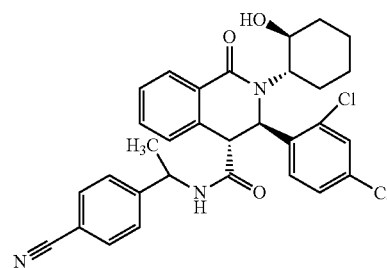


TABLE 253

800

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801

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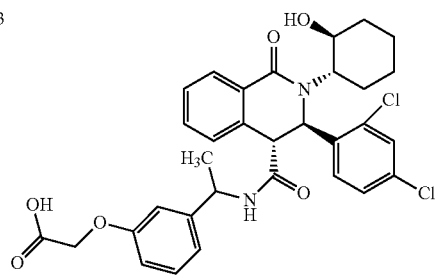
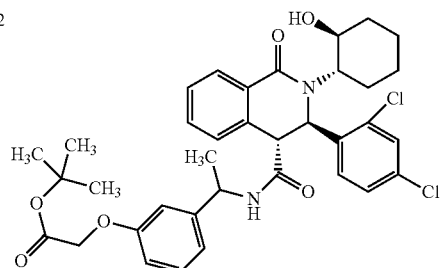
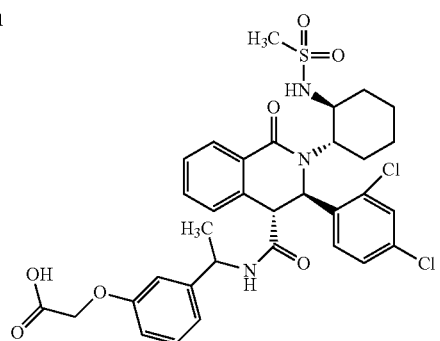
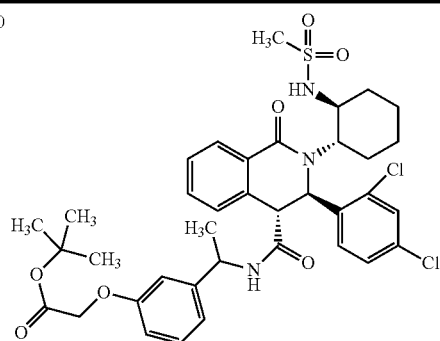
50

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803

60

65



353

TABLE 254

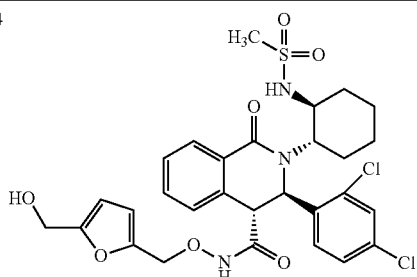
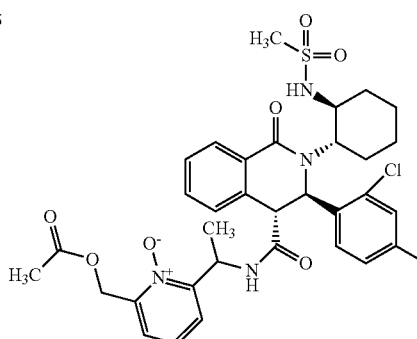
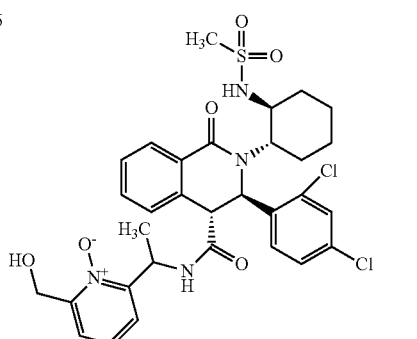
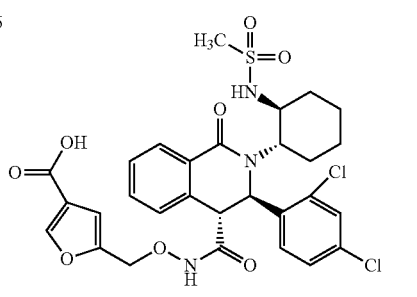
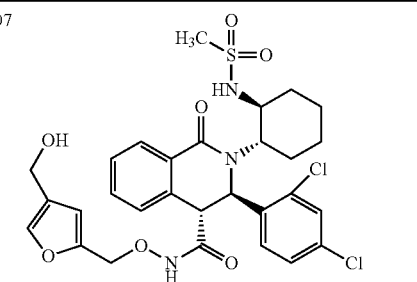
804		racemic mixture
805		chiral compound
56		chiral compound
806		racemic mixture

TABLE 255

807		racemic mixture
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354

TABLE 255-continued

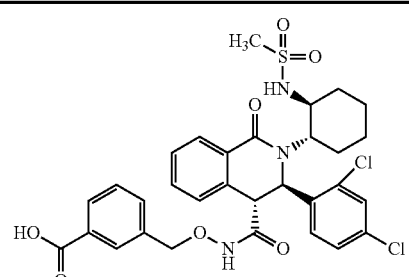
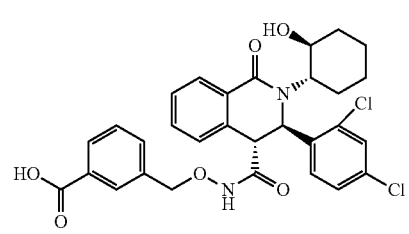
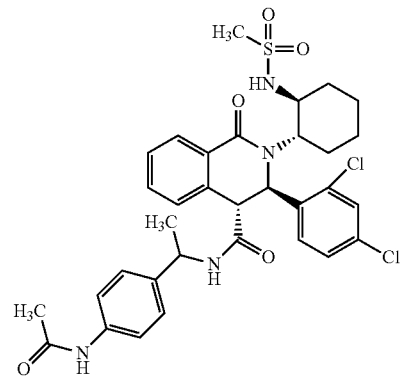
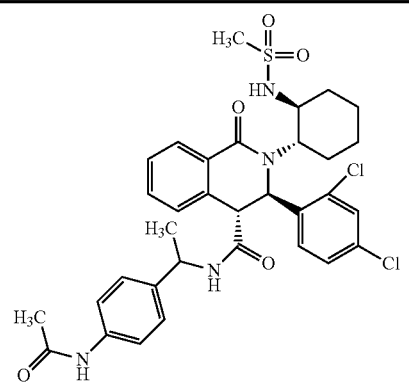
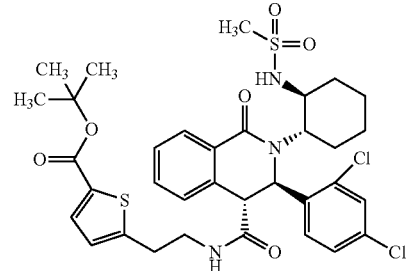
808		racemic mixture
5		
10		
809		racemic mixture
15		
20		
810		chiral compound, diastereomer of Ex811, less polar
25		
30		
35		

TABLE 256

811		chiral compound, diastereomer of Ex810, more polar
45		
50		
55		
812		
60		
65		

355

TABLE 256-continued

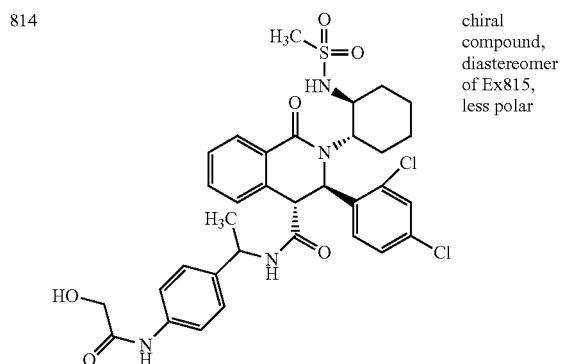
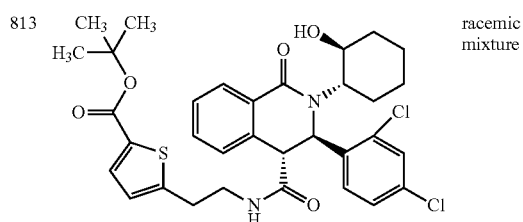


TABLE 257

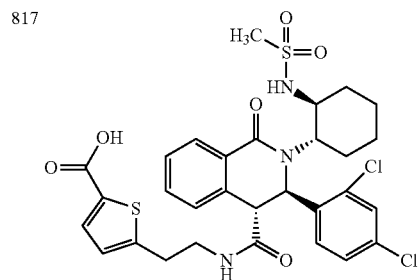
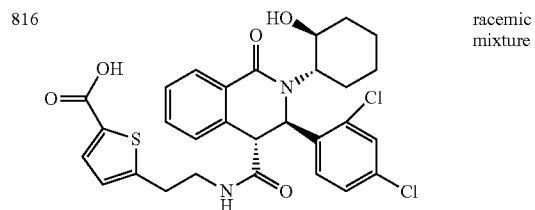
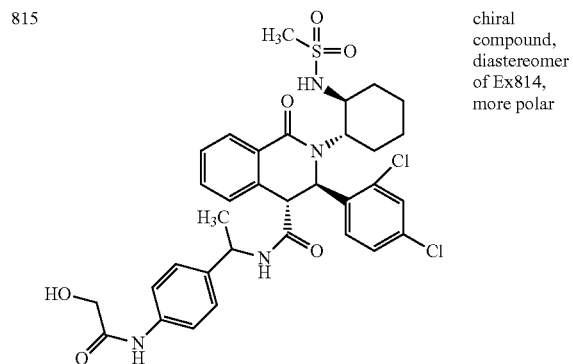
**356**

TABLE 257-continued

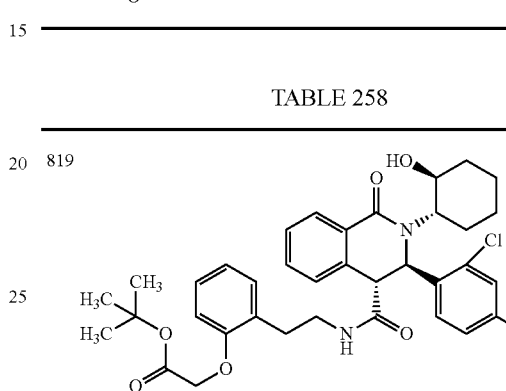
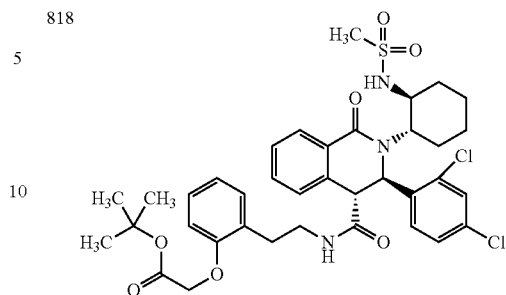
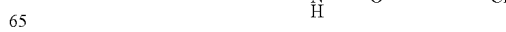
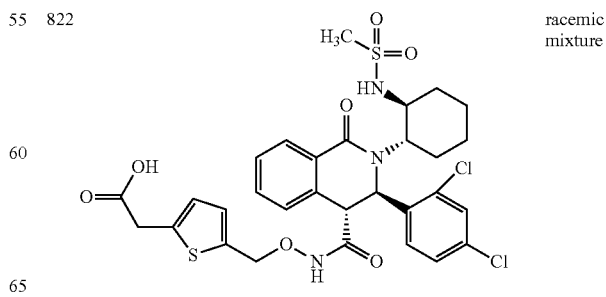
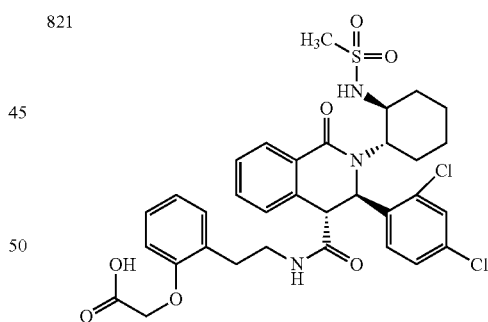
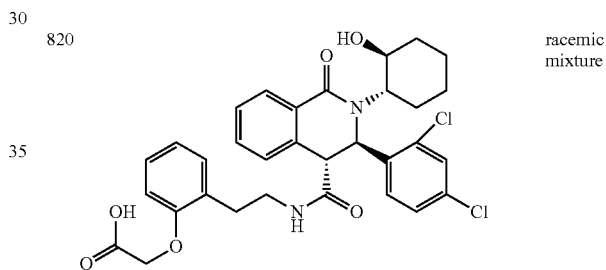
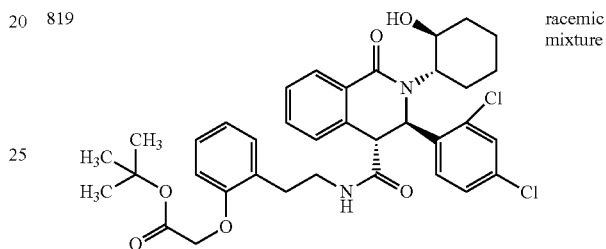


TABLE 258



357

TABLE 259

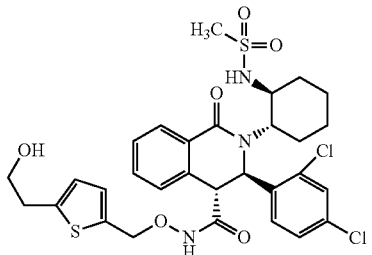
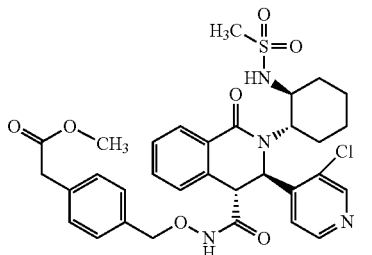
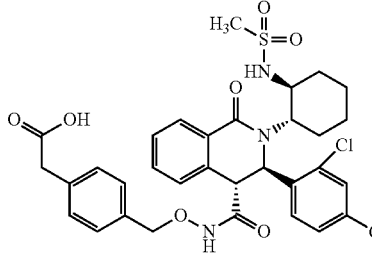
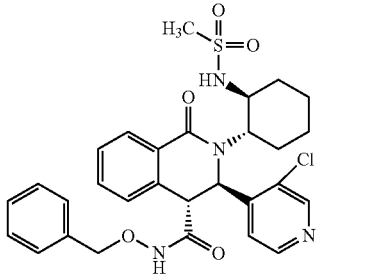
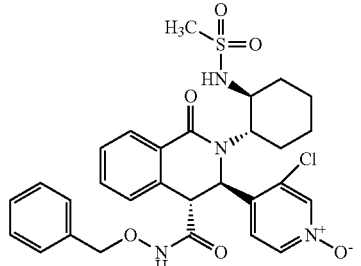
823		racemic mixture
824		racemic mixture
825		racemic mixture
826		racemic mixture

TABLE 260

827		racemic mixture
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358

TABLE 260-continued

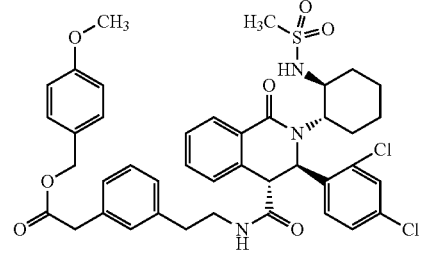
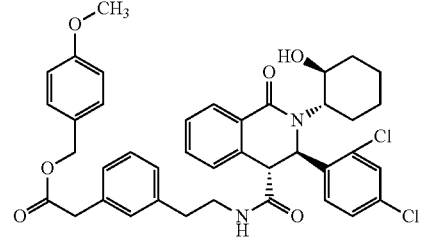
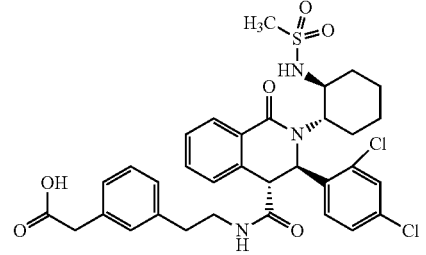
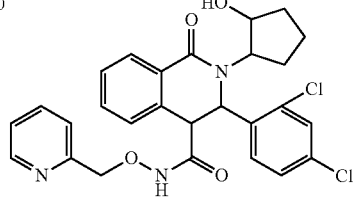
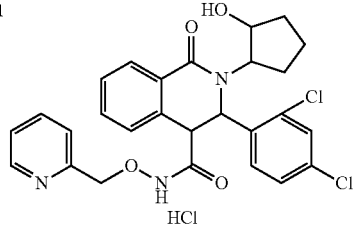
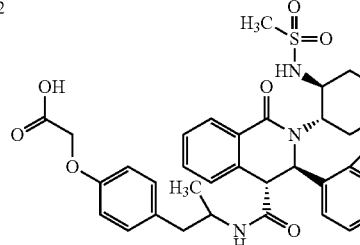
828		
829		racemic mixture
58		

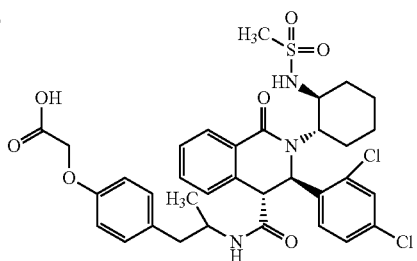
TABLE 261

830		racemic mixture, 1',2'-trans, 3,4-trans, diastereomer of Ex831, more polar
831		racemic mixture, 1',2'-trans, 3,4-trans
832		chiral compound, diastereomer of Ex833, less polar

359

TABLE 261-continued

833

chiral
compound,
diastereomer
of Ex832,
more polar

834

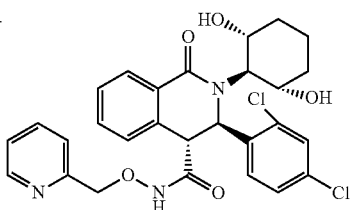
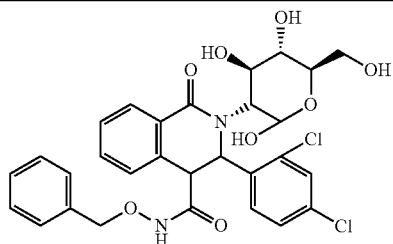
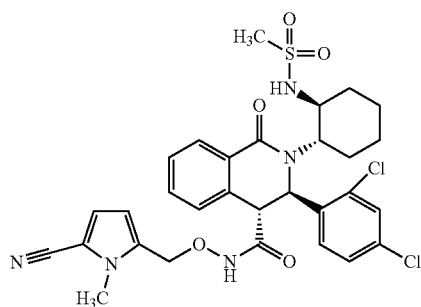
racemic
mixture

TABLE 262

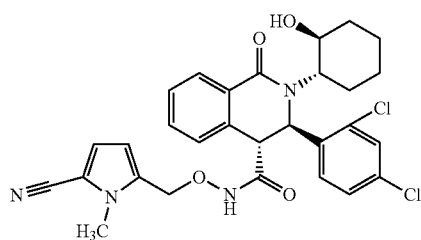
835

diastereo
mixture

836

racemic
mixture

837

racemic
mixture

838

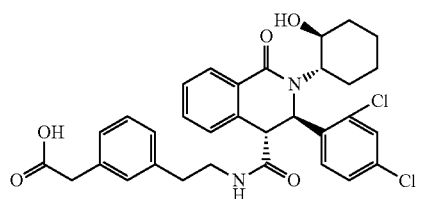
racemic
mixture**360**

TABLE 262-continued

839

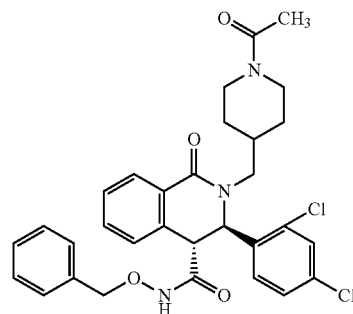
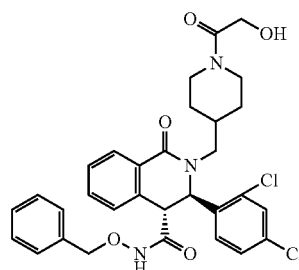
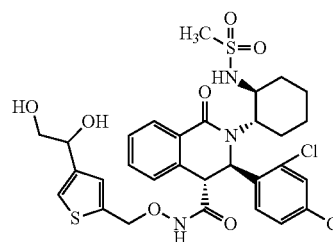
racemic
mixture

TABLE 263

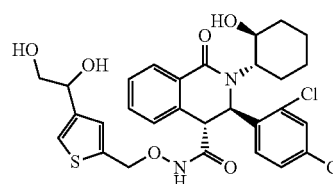
840

racemic
mixture

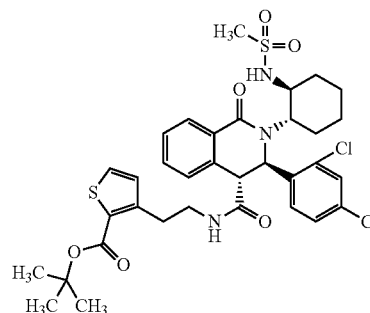
841

diastereo
mixture

842

diastereo
mixture

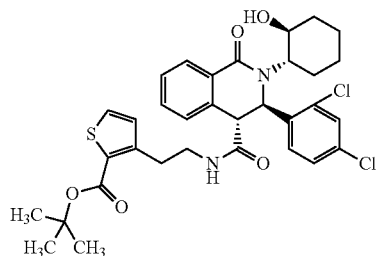
843



361

TABLE 264

844

racemic
mixture

845

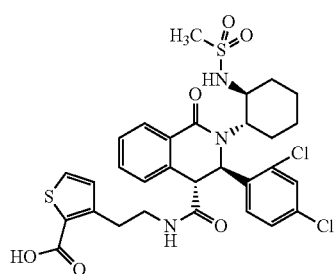
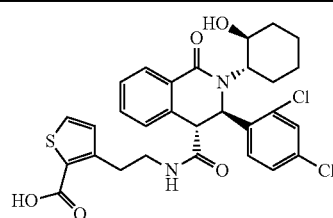
**362**

TABLE 264-continued

846

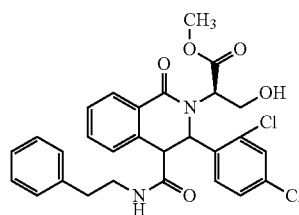
5

racemic
mixture

10

847

15

chiral
compound,
3,4-trans

20

848

25

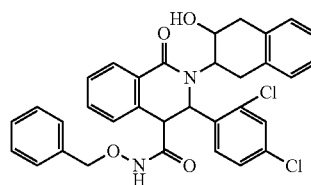
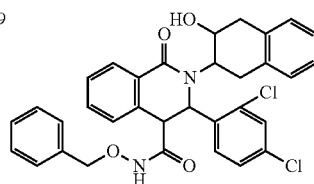
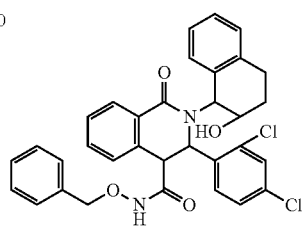
racemic
mixture,
diastereomer
of Ex849,
less polar

TABLE 265

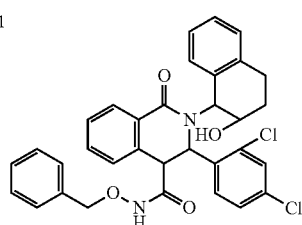
849

racemic
mixture,
diastereomer
of Ex848, more polar

850

racemic
mixture,
diastereomer
of Ex851, less polar

851

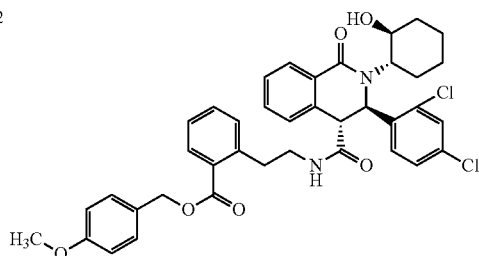
racemic
mixture,
diastereomer
of Ex850, more polar

363

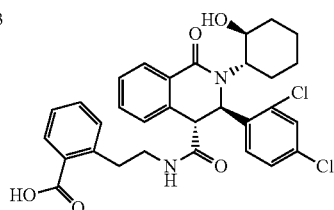
364

TABLE 265-continued

852



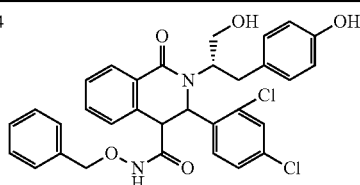
853



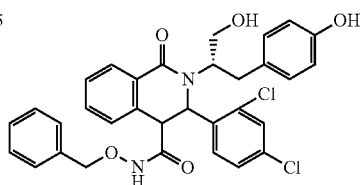
racemic mixture

TABLE 266

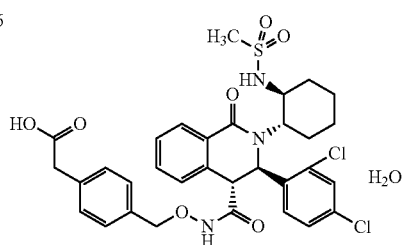
854

chiral compound,
diastereomer
of Ex855,
less polar

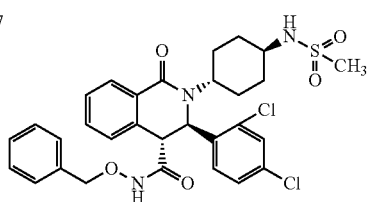
855

chiral compound,
diastereomer
of Ex854,
more polar

856



857

racemic
mixture

858

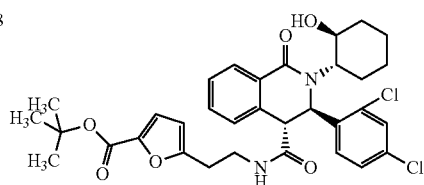
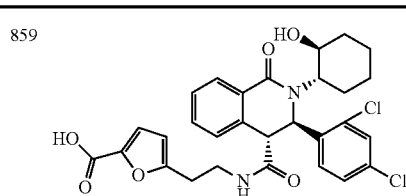
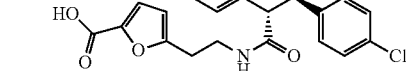
racemic
mixture

TABLE 267

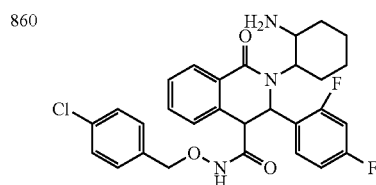
25

racemic
mixture

30



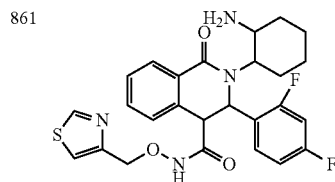
35

racemic
mixture,
1',2'-trans,
3,4-trans

40



45

racemic
mixture,
1',2'-trans,
3,4-trans

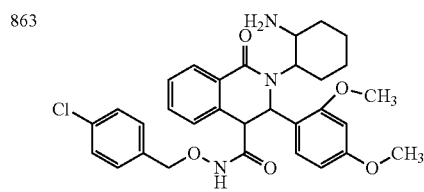
50

racemic
mixture

55



60

racemic
mixture,
1',2'-trans,
3,4-trans

65

365

TABLE 267-continued

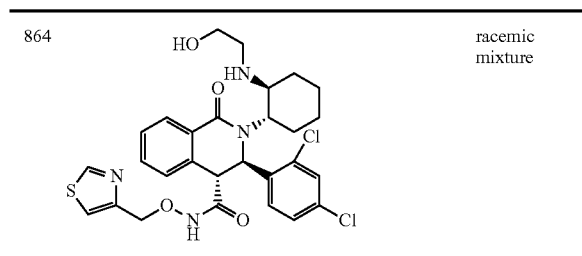


TABLE 268

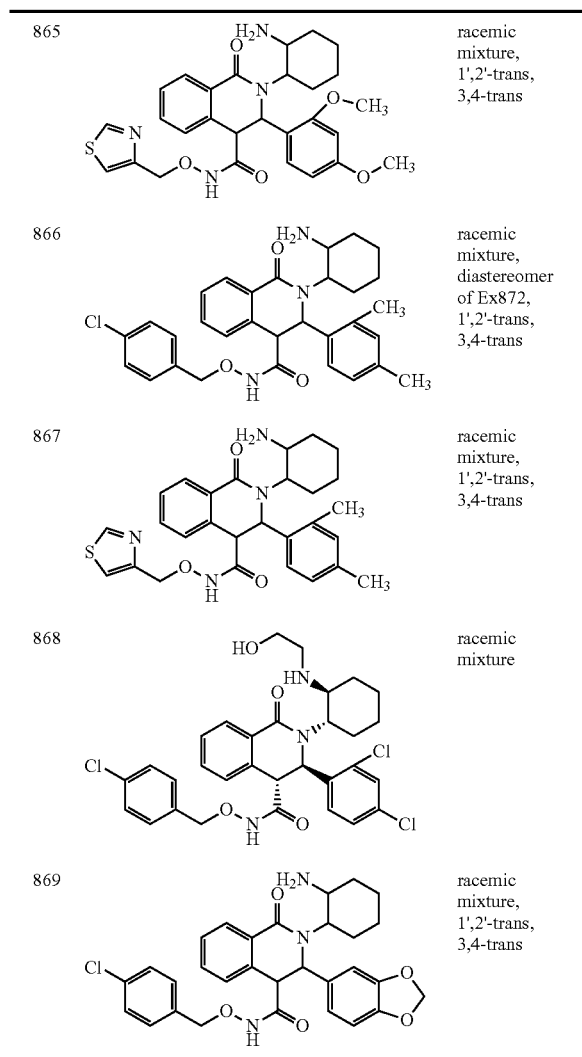
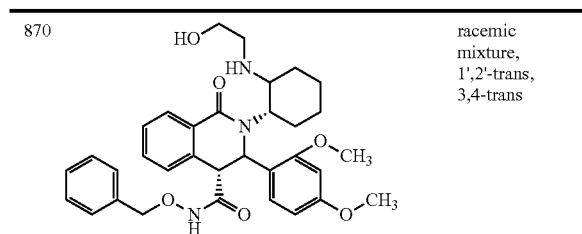


TABLE 269



366

TABLE 269-continued

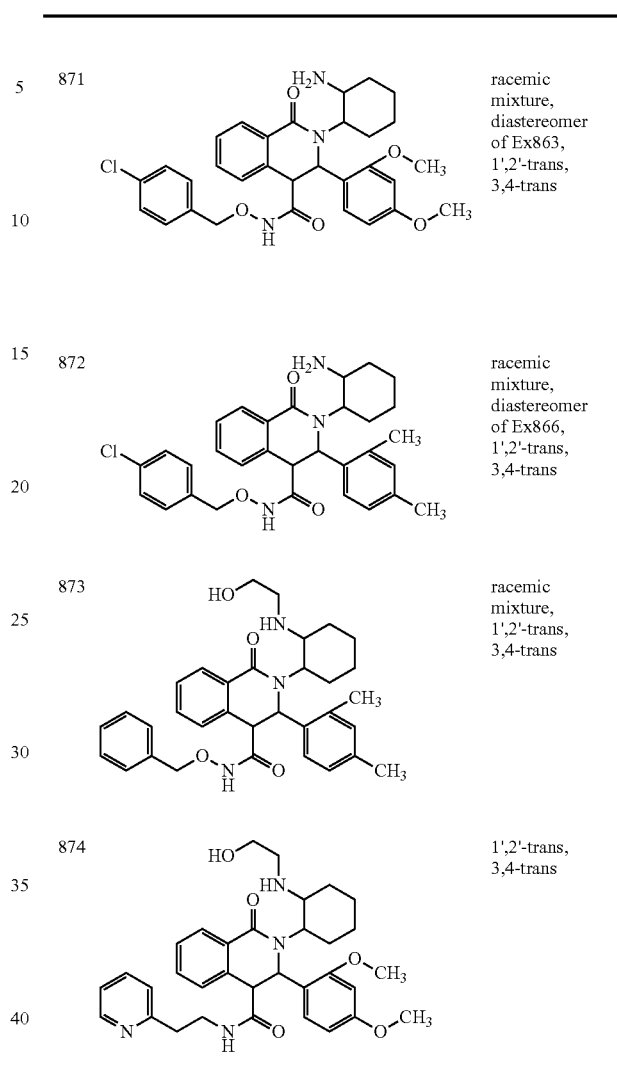
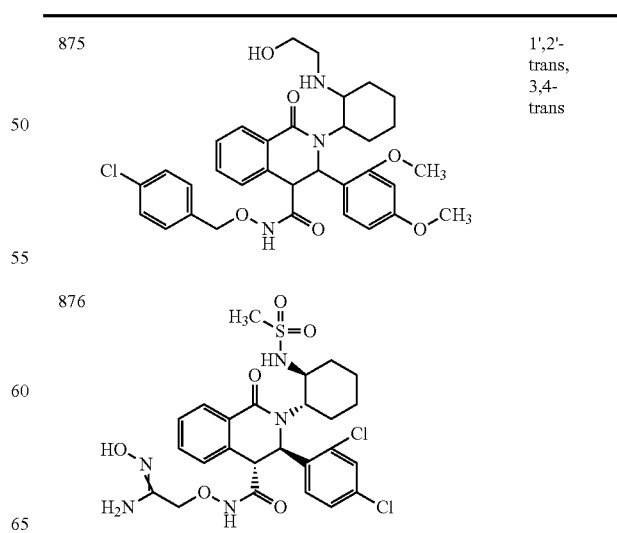


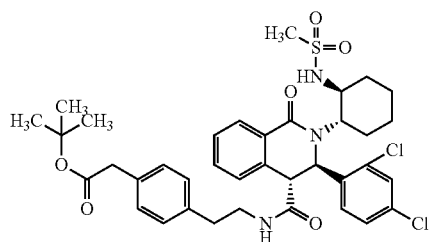
TABLE 270



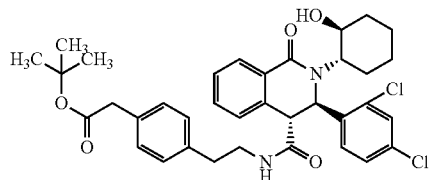
367

TABLE 270-continued

877



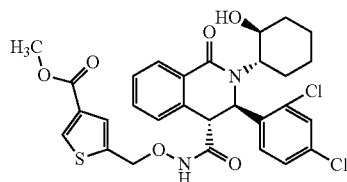
878



racemic mixture

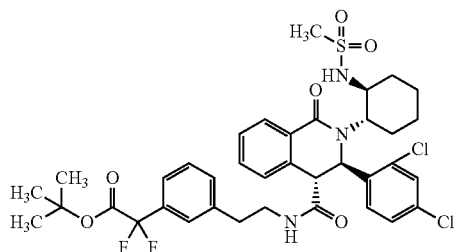
TABLE 271

879

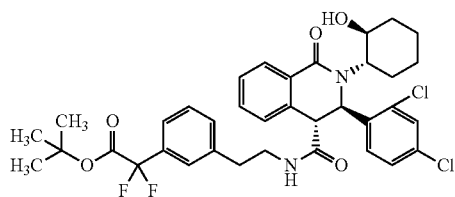


racemic mixture

880

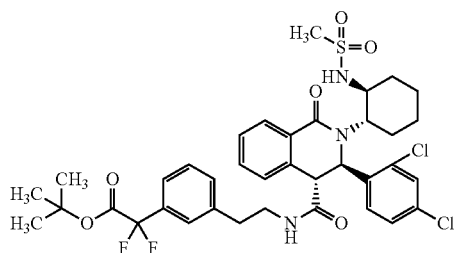


881



racemic mixture

882

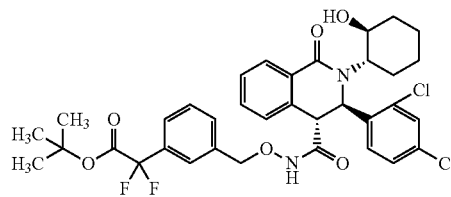


racemic mixture

368

TABLE 271-continued

883



racemic mixture

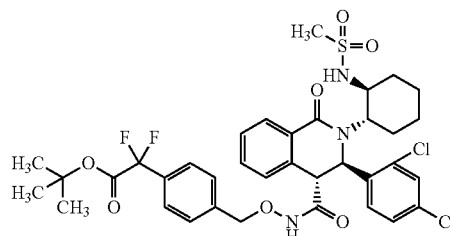
5

10

TABLE 272

15

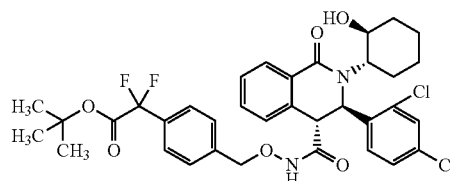
884



20

25

885

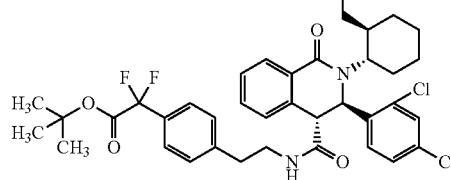


racemic mixture

30

35

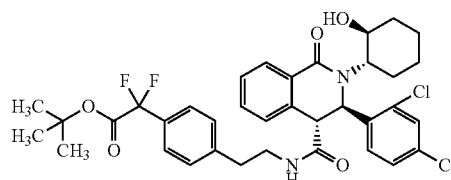
886



40

45

887

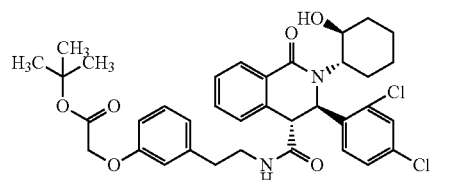


racemic mixture

50

55

888



60

65

371

TABLE 276-continued

Ex	Syn	Data
79	1	FAB+: 525
80	1	FAB+: 503
81	1	FAB+: 565
82	1	FAB+: 511
83	1	FAB+: 467
84	1	ESI+: 499
85	1	FAB+: 491
86	1	FAB+: 539
37	37	FAB+: 560
87	1	FAB+: 533
88	1	FAB+: 503
89	1	FAB+: 511
90	1	FAB+: 525
91	1	FAB+: 483

TABLE 277

92	1	FAB+: 513
93	1	FAB+: 483
94	1	FAB+: 548
95	5	FAB+: 522
96	1	FAB+: 567
97	1	FAB+: 538
98	1	FAB+: 475
99	1	FAB+: 499
100	1	FAB+: 491
101	1	FAB+: 499
102	1	FAB+: 559
103	6	FAB+: 550
104	3	FAB+: 524
105	1	FAB+: 503
106	1	FAB+: 499
107	1	FAB+: 497
108	1	FAB+: 565
2	2	FAB+: 507
109	39	FAB+: 497
39	39	FAB+: 511
110	1	FAB+: 391
111	1	FAB+: 431
4	4	FAB+: 475
112	1	FAB+: 573
113	32	FAB+: 488
114	32	FAB+: 474
115	38	FAB+: 407
116	33	FAB+: 420
117	33	FAB+: 434
118	1	FAB+: 573
119	1	FAB+: 514
120	1	FAB+: 516
121	1	FAB+: 529
122	1	FAB+: 440
123	1	FAB+: 440
124	1	FAB+: 440

TABLE 278

36	36	FAB+: 456
125	36	FAB+: 456
126	36	FAB+: 456
127	1	FAB+: 497
38	38	FAB+: 483
128	38	FAB+: 483
7	7	FAB+: 393
129	1	FAB+: 467
130	10	FAB+: 498
10	10	FAB+: 604
131	10	FAB+: 527
132	3	ESI+: 633
133	3	ESI+: 617
134	3	ESI+: 617
135	3	ESI+: 645
136	3	ESI+: 617
137	3	FAB+: 647

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TABLE 278-continued

138	3	ESI+: 663
139	3	ESI+: 647
140	3	ESI+: 651
141	3	ESI+: 633
142	3	ESI+: 633
143	3	ESI+: 667
144	3	FAB+: 647
145	3	ESI+: 655
146	3	ESI+: 631
147	3	ESI+: 633
NMR1: 1.00-1.90 (7H, m), 2.06-2.23 (1H, m), 2.92 (3H, s), 3.25-3.45 (1H, m), 3.60 (1H, s), 4.12 (1H, brs), 4.90-5.06 (2H, m), 5.21 (1H, s), 6.39 (1H, brs), 6.89 (1H, d, J = 8.4 Hz), 7.04-7.20 (2H, m), 7.27-7.69 (6H, m), 7.87-7.97 (1H, m), 8.29 (1H, d, J = 6.4 Hz), 11.64 (1H, brs)		
9	9	FAB+: 517
148	11	FAB+: 580
149	11	FAB+: 580
11	11	FAB+: 581
150	1	ESI+: 635
151	1	FAB+: 550
152	1	FAB+: 589
153	1	FAB+: 582
154	1	FAB+: 561

TABLE 279

155	1	FAB+: 561
156	1	FAB+: 563
157	1	FAB+: 563
NMR1: 1.19 (3H, d, J = 6.0 Hz), 3.10-3.40 (2H, m), 3.54 (1H, s), 3.99-4.12 (1H, m), 4.34 (1H, brs), 4.46-4.58 (1H, m), 4.80 (2H, brs), 4.90 (1H, brs), 5.75 (1H, s), 6.79 (1H, d, J = 8.4 Hz), 6.99-7.08 (1H, m), 7.17 (1H, d, J = 8.4 Hz), 7.31-7.51 (6H, m), 7.61 (1H, s), 7.96-8.09 (1H, m), 11.63 (1H, brs)		
158	1	FAB+: 523
159	1	FAB+: 498
160	1	FAB+: 498
161	1	FAB+: 555
162	1	FAB+: 551
163	1	FAB+: 552
164	1	FAB+: 538
165	1	FAB+: 636
166	1	FAB+: 579
167	1	FAB+: 482
168	1	FAB+: 536
169	1	FAB+: 510
170	1	FAB+: 540
171	1	FAB+: 553
172	1	FAB+: 578
173	1	FAB+: 552
174	1	FAB+: 583
175	1	FAB+: 565
176	1	FAB+: 579
177	1	FAB+: 549
178	1	FAB+: 538
34	34	FAB+: 647
179	1	FAB+: 551
180	1	FAB+: 664
181	1	FAB+: 555
182	1	FAB+: 539
183	1	FAB+: 555
184	1	FAB+: 540
185	1	FAB+: 668
186	1	FAB+: 668
187	1	FAB+: 547
188	1	FAB+: 540
189	1	FAB+: 505

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TABLE 280

190	1	FAB+: 505	
191	1	FAB+: 499	
192	1	FAB+: 499	
193	1	FAB+: 533	5
194	1	FAB+: 528	
195	1	ESI+: 528	
196	1	ESI+: 561	
197	1	ESI+: 559	
198	1	FAB+: 505	
199	1	FAB+: 505	10
200	1	FAB+: 594	
201	1	FAB+: 594	
202	1	FAB+: 597	
203	1	FAB+: 527	
204	1	ESI+: 534	
205	1	FAB+: 626	15
206	1	FAB+: 610	
207	1	FAB+: 610	
208	1	FAB+: 682	
209	1	FAB+: 682	
210	1	FAB+: 539	
211	1	ESI+: 515	20
212	1	ESI+: 515	
213	1	FAB+: 533	
214	1	ESI-: 541	
215	1	ESI-: 541	
NMR1: 1.16 (3H, d, J = 6.0 Hz), 2.54-2.64 (2H, m), 3.09-3.38 (4H, m), 3.77 (1H, s), 3.99-4.11 (1H, m), 4.27-4.37 (1H, m), 4.52 (1H, brs), 5.13 (1H, d, J = 4.4 Hz), 5.70 (1H, s), 6.65 (2H, d, J = 8.4 Hz), 6.81 (1H, d, J = 8.4 Hz), 6.94 (2H, d, J = 8.4 Hz), 7.11-7.24 (2H, m), 7.36-7.49 (2H, m), 7.60 (1H, d, J = 2.0 Hz), 7.95-8.08 (1H, m), 8.35-8.50 (1H, m), 9.17 (1H, s)			25
216	1	FAB+: 632	30
217	1	FAB+: 533	
218	1	FAB+: 538	
219	1	FAB+: 538	
NMR1: 1.54-1.71 (1H, m), 1.76-1.90 (1H, m), 1.96-2.21 (2H, m), 3.01-3.24 (2H, m), 3.27-3.40 (1H, m), 3.55 (1H, brs), 3.70 (1H, s), 4.70-4.80 (2H, m), 5.25 (1H, s), 7.10-7.18 (1H, m), 7.22 (1H, dd, J = 2.4, 8.4 Hz), 7.30-7.47 (7H, m), 7.52 (1H, d, J = 8.4 Hz), 7.62 (1H, d, J = 2.0 Hz), 7.82-7.90 (1H, m), 11.34 (1H, s)			35

TABLE 281

220	1	FAB+: 610	
221	1	FAB+: 573	
222	1	FAB+: 529	45
223	1	ESI-: 527	
224	1	ESI+: 541	
225	1	FAB+: 561	
226	1	FAB+: 616	
227	1	FAB+: 549	
228	1	FAB+: 664	50
229	1	FAB+: 679	
230	1	FAB+: 679	
231	1	FAB+: 602	
232	1	ESI+: 680	
233	1	ESI+: 694	
234	1	FAB+: 678	55
235	1	ESI+: 674	
236	1	FAB+: 614	
237	1	FAB+: 614	
238	1	FAB+: 693	
239	1	FAB+: 659	
240	1	FAB+: 587	60
241	1	FAB+: 694	
242	1	FAB+: 587	
243	1	ESI+: 675	
244	1	FAB+: 670	
245	1	ESI+: 602	
246	1	ESI+: 607	65
247	1	ESI+: 672	
248	R38	ESI+: 574	

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TABLE 281-continued

	1	
249	R38	FAB+: 573
	1	
250	1	FAB+: 567
251	1	FAB+: 566
252	1	ESI+: 658
253	1	ESI+: 658
254	1	FAB+: 632
255	1	FAB+: 585
256	1	FAB+: 584
257	1	FAB+: 674
258	1	ESI+: 658

TABLE 282

259	1	FAB+: 630
260	1	FAB+: 639
261	1	ESI+: 603
262	1	FAB+: 600
263	1	FAB+: 607
264	1	FAB+: 628
265	1	FAB+: 616
266	1	FAB+: 616
267	1	ESI+: 603
268	1	ESI+: 631
269	1	FAB+: 629
270	1	FAB+: 617
271	1	FAB+: 577
272	1	FAB+: 554
273	1	ESI+: 601
274	1	FAB+: 601
275	1	FAB+: 577
276	1	ESI+: 602
277	1	ESI+: 539
278	1	ESI+: 539
279	1	FAB+: 601
280	1	ESI+: 554
281	1	FAB+: 624
282	1	ESI-: 626
283	1	FAB+: 582
284	1	ESI+: 593
285	1	ESI+: 593
286	1	FAB+: 592
287	1	FAB+: 592
288	1	FAB+: 498
289	1	FAB+: 530
290	1	FAB+: 530
291	1	FAB+: 704
292	1	FAB+: 502
293	1	FAB+: 529
294	1	ESI-: 527
295	1	FAB+: 638
296	1	FAB+: 630
297	1	FAB+: 633
298	1	FAB+: 744
299	1	FAB+: 746

TABLE 283

300	1	ESI+: 718
301	1	FAB+: 730
302	1	FAB+: 647
303	1	ESI+: 633
304	1	FAB+: 751
305	1	ESI+: 688
306	1	ESI+: 647
307	1	ESI+: 723
308	1	FAB+: 730
309	1	FAB+: 652
310	1	FAB+: 638
311	1	FAB+: 710
312	1	ESI+: 849
313	1	ESI+: 660
314	1	ESI+: 673
315	1	FAB+: 647

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TABLE 283-continued

316	1	FAB+: 647	
317	1	ESI+: 730	
318	1	ESI+: 656	
319	1	FAB+: 730	5
320	1	ESI+: 728	
321	1	ESI+: 618	
322	1	FAB+: 688	
323	1	FAB+: 692	
324	1	FAB+: 704	
325	1	FAB+: 704	10
326	1	FAB+: 634	
327	1	FAB+: 702	
328	1	FAB+: 617	
329	1	ESI+: 674	
330	1	FAB+: 680	
331	1	FAB+: 635	15
332	1	FAB+: 608	
333	1	ESI+: 688	
334	1	FAB+: 622	
335	1	ESI+: 631	
336	1	FAB+: 617	
337	1	FAB+: 617	20
338	1	ESI+: 660	
339	1	FAB+: 635	
340	1	ESI+: 622	

TABLE 284

341	1	FAB+: 647	
342	1	FAB+: 563	
343	1	FAB+: 563	
344	1	FAB+: 635	
345	1	ESI+: 660	30
346	1	FAB+: 631	
347	1	ESI+: 622	
348	1	ESI+: 647	
349	1	ESI+: 673	
350	1	ESI+: 606	
351	1	FAB+: 620	35
352	1	ESI+: 632	
353	1	FAB+: 619	
354	1	ESI+: 568	
355	1	FAB+: 620	
356	1	FAB+: 642	
357	1	FAB+: 622	40
358	1	ESI+: 631	
359	1	ESI+: 680	
360	1	ESI+: 565	
361	1	FAB+: 607	
362	1	ESI+: 591	45
363	1	ESI+: 642	
364	1	FAB+: 613	
365	1	ESI+: 651	
366	1	FAB+: 657	
367	1	FAB+: 637	
368	1	FAB+: 631	
369	1	ESI+: 637	50
370	1	FAB+: 623	
371	1	FAB+: 631	
372	1	ESI+: 618	
373	1	ESI+: 688	
374	1	FAB+: 631	
375	1	FAB+: 601	55
376	1	FAB+: 702	
377	1	FAB+: 601	
378	1	ESI+: 647	
379	1	ESI+: 643	
380	1	FAB+: 654	
381	1	ESI+: 602	60

TABLE 285

382	1	FAB+: 630	
383	1	FAB+: 657	65
384	1	FAB+: 587	

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TABLE 285-continued

385	1	FAB+: 587	
386	1	FAB+: 630	
387	1	FAB+: 630	
388	1	FAB+: 631	
389	1	FAB+: 671	
390	1	ESI+: 679	
391	1	FAB+: 640	
392	1	ESI+: 647	
393	1	FAB+: 608	
394	1	ESI+: 643	
395	1	FAB+: 660	
396	1	ESI+: 602	
397	1	ESI+: 602	
398	1	ESI+: 640	
399	1	ESI+: 641	
400	1	FAB+: 538	
401	1	FAB+: 538	
NMR1: 1.54-1.71 (1H, m), 1.75-1.89 (1H, m), 1.97-2.21 (2H, m), 2.99-3.25 (2H, m), 3.26-3.41 (1H, m), 3.55 (1H, brs), 3.70 (1H, s), 4.67-4.82 (2H, m), 5.25 (1H, s), 7.10-7.18 (1H, m), 7.22 (1H, dd, J = 2.4, 8.4 Hz), 7.27-7.40 (7H, m), 7.52 (1H, d, J = 8.4 Hz), 7.62 (1H, d, J = 2.0 Hz), 7.80-7.90 (1H, m), 11.34 (1H, s)			
402	1	ESI+: 528	
403	1	FAB+: 547	25
404	1	ESI+: 528	
405	1	FAB+: 569	
406	1	FAB+: 582	
407	1	FAB+: 529	
408	1	FAB+: 529	
409	1	FAB+: 527	30
410	1	FAB+: 539	
411	1	FAB+: 539	
412	1	ESI+: 593	
413	1	FAB+: 540	
414	1	FAB+: 668	
415	1	FAB+: 540	35
416	1	FAB+: 592	
417	1	FAB+: 592	

TABLE 286

418	1	FAB+: 592	
419	1	FAB+: 592	
420	1	FAB+: 537	
421	1	FAB+: 537	
422	1	FAB+: 551	
423	1	FAB+: 540	45
424	1	FAB+: 539	
425	1	FAB+: 587	
426	1	FAB+: 575	
427	1	FAB+: 566	
428	1	FAB+: 551	
429	1	FAB+: 530	50
430	1	FAB+: 510	
431	1	FAB+: 538	
432	1	FAB+: 508	
433	1	FAB+: 608	
434	1	FAB+: 538	
435	1	FAB+: 601	55
436	1	FAB+: 587	
437	1	FAB+: 613	
438	1	FAB+: 674	
439	1	FAB+: 539	
440	1	FAB+: 593	
441	1	FAB+: 500	60
442	1	FAB+: 499	
443	1	FAB+: 530	
444	1	FAB+: 540	
445	1	FAB+: 530	
446	1	FAB+: 530	
447	1	FAB+: 530	65
448	1	FAB+: 530	
449	1	FAB+: 596	

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TABLE 286-continued

450	1	FAB+: 540
451	1	ESI+: 515
452	1	FAB+: 540
453	1	FAB+: 596
454	1	ESI+: 595
455	1	ESI+: 595
456	1	ESI+: 595
457	1	ESI+: 595
458	1	FAB+: 571

TABLE 287

459	1	FAB+: 571
460	1	FAB+: 538
461	1	FAB+: 605
462	1	ESI+: 618
463	1	ESI+: 606
464	1	ESI+: 746
465	1	ESI+: 690
466	1	ESI+: 703
467	1	ESI+: 692
468	1	ESI+: 746
469	1	ESI+: 732
470	1	ESI+: 718
471	1	ESI+: 692
472	1	ESI+: 692
473	1	FAB+: 642
474	1	ESI+: 732
475	1	ESI+: 606
476	1	ESI+: 746
477	1	FAB+: 618
478	1	ESI+: 638
479	1	ESI+: 692
480	1	ESI+: 605
481	1	FAB+: 543
482	1	ESI+: 557
483	1	FAB+: 571
484	1	FAB+: 674
485	1	ESI+: 674
486	1	FAB+: 597
487	1	FAB+: 553
488	1	FAB+: 597
489	1	FAB+: 589
490	1	FAB+: 576
491	1	FAB+: 567
492	1	FAB+: 545
493	1	FAB+: 546
494	1	ESI+: 567
495	1	FAB+: 567
496	1	FAB+: 567
497	1	FAB+: 607
498	1	FAB+: 553
499	1	ESI+: 573

TABLE 288

500	1	FAB+: 573
501	1	ESI+: 592
502	1	FAB+: 603
503	1	ESI+: 565
504	1	FAB+: 565
505	1	FAB+: 573
506	1	FAB+: 505
507	1	ESI+: 557
508	32	FAB+: 623
509	32	ESI+: 659
510	32	FAB+: 610
511	32	ESI+: 582
512	32	ESI+: 596
513	32	FAB+: 610
514	32	FAB+: 582
515	32	FAB+: 596
516	33	FAB+: 496
	34	FAB+: 581

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TABLE 288-continued

517	34	FAB+: 567
518	34	FAB+: 595
519	34	FAB+: 595
520	34	FAB+: 611
521	34	FAB+: 637
522	34	FAB+: 638
523	34	FAB+: 650
524	34	FAB+: 596
525	34	FAB+: 609
526	34	ESI+: 627
527	35	FAB+: 596
528	4	ESI+: 674
529	4	ESI+: 571
NMR1: 1.19 (3H, d, J = 6.0 Hz), 3.12-3.48 (2H, m), 3.55 (1H, s), 4.01-4.13 (1H, m), 4.28-4.38 (1H, m), 4.47-4.60 (1H, m), 4.80-4.97 (3H, m), 5.73 (1H, s), 6.79 (1H, d, J = 8.4 Hz), 7.01-7.09 (1H, m), 7.17 (1H, dd, J = 2.0, 8.4 Hz), 7.39-7.69 (5H, m), 7.91-8.08 (3H, m), 11.67 (1H, s), 13.04 (1H, brs)		
530	4	ESI+: 661
531	4	ESI+: 571
532	4	FAB+: 644

TABLE 289

533	4	ESI+: 666
534	4	ESI+: 666
535	4	ESI+: 665
536	4	ESI+: 645
537	4	FAB+: 688
538	4	ESI+: 688
539	4	ESI+: 690
540	4	ESI+: 674
541	4	ESI+: 674
NMR1: 1.00-2.30 (8H, m), 2.94 (3H, s), 3.58 (3H, s), 4.07 (1H, brs), 4.74 (1H, d, J = 11.0 Hz), 4.77 (1H, d, J = 11.0 Hz), 5.18 (1H, s), 6.36 (1H, d, J = 6.9 Hz), 6.88 (1H, d, J = 8.4 Hz), 7.08-7.11 (1H, m), 7.16 (1H, d, J = 2.0 Hz), 7.18 (1H, d, J = 2.0 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.43-7.48 (2H, m), 7.64 (1H, d, J = 2.0 Hz) 7.93-7.96 (1H, m), 11.42 (1H, s), 12.34 (1H, brs)		
542	4	FAB+: 710
NMR1: 0.48-0.71 (1H, m), 1.01-1.37 (4H, m), 1.40-1.65 (2H, m), 2.46-2.59 (1H, m), 2.78 (3H, s), 3.15-3.50 (2H, m), 4.66-4.84 (3H, m), 5.17 (1H, s), 6.68 (1H, d, J = 8.4 Hz), 7.02-7.09 (1H, m), 7.12-7.20 (3H, m), 7.27-7.40 (2H, m), 7.46 (1H, d, J = 0.8 Hz), 7.64 (1H, d, J = 8.0 Hz), 8.57 (1H, brs)		
543	4	ESI+: 718
544	4	ESI+: 702
545	4	ESI+: 702
546	4	FAB+: 638
547	4	FAB+: 624
548	4	ESI+: 702
549	4	ESI+: 676
550	4	ESI+: 674
551	4	ESI+: 640
552	4	ESI+: 678
553	4	ESI+: 688
554	4	ESI+: 690
555	4	FAB+: 660
556	4	ESI+: 660
557	4	ESI+: 666
558	4	FAB+: 620
559	4	ESI+: 596
560	4	ESI+: 660
561	4	FAB+: 583
562	4	ESI+: 583

TABLE 290

563	4	ESI+: 660
564	4	ESI+: 660
565	4	ESI+: 678
566	4	FAB+: 678

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TABLE 290-continued

567	4	ESI+: 690	5
568	4	FAB+: 718	
569	4	ESI+: 647	
570	4	ESI+: 678	
571	4	FAB+: 678	
572	38	FAB+: 592	10
573	39	ESI+: 569	
574	39	ESI+: 582	
575	39	ESI+: 602	
576	39	FAB+: 565	
577	39	FAB+: 636	15
578	39	FAB+: 573	
16	16	FAB+: 579	
15	15	ESI-: 579	
22	22	ESI+: 716	
43	43	FAB+: 680	20
29	29	ESI+: 666	
23	23	ESI+: 700	
41	41	FAB+: 624	
579	23	ESI+: 830	
13	13	FAB+: 617	25
580	13	FAB+: 609	
581	13	FAB+: 577	
582	13	FAB+: 577	
583	13	FAB+: 618	
14	14	FAB+: 645	30
584	12	FAB+: 576	
12	12	FAB+: 616	
585	12	FAB+: 617	
586	12	ESI+: 617	
587	12	FAB+: 608	35
588	12	FAB+: 678	
589	12	ESI+: 617	
590	12	FAB+: 615	
591	12	FAB+: 562	
592	12	FAB+: 630	40
593	12	FAB+: 616	

TABLE 291

594	12	FAB+: 608	45
595	12	FAB+: 580	
596	12	FAB+: 610	
18	18	ESI+: 684	
597	18	FAB+: 592	
598	18	ESI+: 606	50
599	18	ESI+: 606	
600	18	ESI+: 608	
21	21	ESI+: 598	
601	21	ESI+: 674	
20	20	ESI+: 737	55
27	27	FAB+: 593	
40	40	ESI-: 568	
602	40	FAB+: 569	
8	8	FAB+: 577	
603	6	FAB+: 566	60
604	6	FAB+: 540	
605	6	FAB+: 540	
606	6	FAB+: 524	
6	6	FAB+: 564	
607	6	FAB+: 524	65
42	42	ESI+: 648	
31	31	FAB+: 638	
608	5	ESI+: 526	
609	5	ESI+: 484	
610	5	FAB+: 538	70
611	5	FAB+: 582	
612	5	ESI+: 510	
613	5	ESI+: 510	
614	5	ESI+: 510	
615	5	ESI+: 510	75
616	5	FAB+: 582	
617	5	FAB+: 508	
618	5	FAB+: 508	
619	5	FAB+: 536	
620	5	FAB+: 536	80
5	5	FAB+: 482	

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TABLE 291-continued

621	5	FAB+: 538
30	30	FAB+: 632
622	30	ESI+: 648
623	28	FAB+: 568

TABLE 292

28	28	FAB+: 568
624	28	FAB+: 568
24	24	ESI+: 607
625	19	ESI+: 632
626	19	FAB+: 674
627	19	ESI+: 672
628	19	ESI+: 688
629	19	FAB+: 654
630	19	FAB+: 674
631	19	ESI+: 690
632	19	ESI+: 584
633	19	ESI+: 613
19	19	ESI+: 690
634	19	ESI+: 647
635	19	ESI+: 632
636	19	FAB+: 690
25	25	ESI+: 633
637	25	FAB+: 690
26	26	FAB+: 526
17-2	17	FAB+: 568
17-1	17	FAB+: 550
638	1	ESI+: 724
639	1	ESI+: 780
640	53	ESI+: 650
53	53	ESI+: 664
641	30	ESI+: 648
642	1	ESI+: 662
45	45	ESI+: 632
643	4	ESI+: 676
644	1	ESI+: 623
645	1	ESI+: 748
646	1	ESI+: 704
647	1	ESI+: 688
648	1	FAB+: 676
	4	
649	1	ESI+: 690
	4	
650	4	FAB+: 718
651	3	FAB+: 767
52	52	ESI+: 663

TABLE 293

652	19	ESI+: 648
653	1	FAB+: 611
	19	
654	4	ESI+: 674
655	1	ESI+: 674
	4	
656	1	FAB+: 615
657	1	FAB+: 615
51	51	ESI+: 598
658	1	FAB+: 665
659	3	ESI+: 631
660	1	ESI+: 695
661	43	ESI+: 624
662	41	ESI+: 680
663	55	ESI+: 638
664	20	ESI+: 767
665	6	ESI+: 703
	12	
666	4	ESI+: 651
667	3	ESI+: 631
668	39	ESI+: 675
46	46	FAB+: 660
669	1	FAB+: 673
670	1	ESI+: 721
47	47	ESI+: 624

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TABLE 293-continued

671	1	ESI+: 704	
672	1	FAB+: 672	
673	1	ESI+: 731	
674	1	ESI+: 710	5
	19		
675	19	ESI+: 648	
676	19	FAB+: 675	
677	1	ESI+: 695	
678	1	ESI+: 735	
679	1	ESI+: 710	10
	19		
680	1	ESI+: 688	
	19		
681	P8	ESI-: 675	
	P9		15
	1		

TABLE 294

682	1	FAB+: 658	
683	4	ESI+: 663	
684	1	FAB+: 611	
49	49	FAB+: 689	
685	3	FAB+: 705	
686	4	FAB+: 597	
687	1	FAB+: 633	
688	1	ESI+: 731	
55	55	FAB+: 663	
689	1	FAB+: 703	
690	20	FAB+: 674	
691	19	ESI+: 675	
692	1	ESI+: 744	
693	19	ESI+: 688	
54	54	ESI+: 663	
694	3	FAB+: 719	
695	1	FAB+: 752	
696	P38	ESI+: 714	
	1		
697	54	FAB+: 679	
698	52	ESI+: 648	
699	4	FAB+: 700	
700	1	ESI+: 735	
		NMR1: 0.99-1.85 (8H, m), 2.10-2.24 (1H, m), 2.69-2.83 (2H, m), 2.92 (3H, s), 3.25-3.45 (5H, m), 3.73 (1H, s), 3.95 (1H, brs), 5.21 (1H, s), 6.41-6.51 (1H, m), 6.85 (1H, d, J = 8.0 Hz), 7.11-7.22 (2H, m), 7.35-7.48 (4H, m), 7.64 (1H, d, J = 2.0 Hz), 7.73-7.81 (2H, m), 7.88-7.96 (1H, m), 8.07 (1H, brs), 12.08 (1H, brs)	
701	19	ESI+: 672	
		NMR1: 0.99-1.87 (8H, m), 2.11-2.26 (1H, m), 2.59-2.74 (2H, m), 2.91 (3H, s), 3.18-3.40 (2H, m), 3.51 (2H, s), 3.75 (1H, s), 3.93 (1H, brs), 5.24 (1H, s), 6.41-6.54 (1H, m), 6.85 (1H, d, J = 8.0 Hz), 7.01-7.23 (6H, m), 7.39-7.48 (2H, m), 7.65 (1H, d, J = 2.0 Hz), 7.89-7.98 (1H, m), 8.08 (1H, brs), 12.28 (1H, brs)	
702	19	FAB+: 595	
703	4	FAB+: 589	
704	1	ESI+: 669	
705	1	FAB+: 555	
706	1	ESI+: 746	
707	1	FAB+: 531	
708	1	ESI+: 678	

TABLE 295

44	44	ESI-: 650	
709	4	FAB+: 718	
		NMR1: 1.09 (2H, t, J = 6.9 Hz), 1.00-2.00 (5H, m), 2.10-2.25 (1H, m), 2.40 (2H, t, J = 7.2 Hz), 2.94 (3H, s), 3.18-3.50 (3H, m), 3.57 (1H, s), 3.98 (1H, t, J = 6.3 Hz), 4.73 (1H, d, J = 11.3 Hz), 4.78 (1H, d, J = 11.3 Hz), 5.16 (1H, s), 6.32-6.38 (1H, m), 6.85-6.95 (3H, m), 7.05-7.50 (3H, m), 7.39-7.48 (2H, m), 7.63 (1H, d, J = 2.0 Hz), 7.89-7.98 (1H, m), 11.39 (1H, brs)	

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TABLE 295-continued

710	1	ESI+: 751	
711	19	ESI+: 708	
712	19	ESI+: 708	
		NMR1: 0.99-1.87 (8H, m), 2.11-2.26 (1H, m), 2.59-2.74 (2H, m), 2.91 (3H, s), 3.18-3.40 (2H, m), 3.51 (2H, s), 3.75 (1H, s), 3.93 (1H, brs), 5.24 (1H, s), 6.41-6.54 (1H, m), 6.85 (1H, d, J = 8.0 Hz), 7.01-7.23 (6H, m), 7.39-7.48 (2H, m), 7.65 (1H, d, J = 2.0 Hz), 7.89-7.98 (1H, m), 8.08 (1H, brs), 12.28 (1H, brs)	
713	19	ESI+: 631	
714	19	ESI+: 633	
715	3	ESI+: 767	
57	57	ESI+: 701	
716	4	FAB+: 650	
717	32	ESI+: 596	
718	52	ESI+: 663	
719	1	FAB+: 596	
720	1	ESI+: 572	
721	4	ESI+: 641	
722	32	FAB+: 610	
723	21	ESI+: 596	20
724	21	FAB+: 596	
725	1	FAB+: 751	
726	1	ESI+: 639	
727	1	ESI+: 639	
728	P9	ESI+: 617	
	P40		25
	1		
729	41	ESI+: 622	
730	52	ESI+: 647	
731	3	FAB+: 767	
732	52	FAB+: 663	
733	41	ESI+: 622	30
734	18	ESI+: 682	
735	18	ESI+: 682	

TABLE 296

736	21	ESI+: 672	
737	41	ESI+: 698	
738	21	ESI+: 672	
739	4	ESI+: 589	
740	44	ESI-: 650	
741	1	ESI+: 782	
742	1	ESI+: 538	
743	1	ESI+: 538	
744	3	ESI+: 554	
745	44	ESI-: 573	
746	1	ESI+: 555	
747	1	ESI+: 563	
748	21	ESI+: 596	
59	59	ESI+: 681	
749	3	ESI+: 554	
750	41	ESI+: 622	
751	19	ESI-: 623	
752	19	FAB+: 710	
753	19	ESI+: 633	
754	19	ESI+: 708	
755	19	ESI+: 631	
756	1	ESI+: 645	
757	1	ESI+: 645	
758	1	ESI+: 644	
50	50	ESI+: 687	
759	1	ESI+: 731	
760	1	ESI+: 706	
761	19	ESI-: 609	
762	19	FAB+: 675	
763	19	ESI+: 650	60
764	1	ESI+: 709	
765	1	ESI-: 656	
766	1	ESI+: 678	
767	44	ESI+: 667	
768	4	FAB+: 664	
769	44	ESI+: 650	65
770	1	ESI+: 720	

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TABLE 296-continued

771	1	ESI+: 643
772	19	ESI+: 587
773	19	ESI+: 664
774	1	ESI+: 779

TABLE 297

775	1	ESI+: 706
776	P8	ESI+: 633
	P9	
	1	
777	35	ESI+: 597
48	48	ESI+: 689
778	19	ESI+: 650
779	1	FAB+: 633
780	1	ESI+: 661
781	4	ESI+: 619
782	1	ESI-: 577
783	1	ESI+: 631
784	1	ESI+: 631
785	48	ESI+: 601
786	48	ESI+: 601
787	1	ESI+: 672
	19	
788	21	ESI+: 612
789	3	ESI+: 613
790	4	ESI+: 647
791	19	ESI+: 617
792	19	ESI+: 617
793	P9	ESI+: 678
	1	
794	1	ESI+: 714
795	19	ESI+: 658
796	19	ESI+: 658
797	41	ESI+: 638
798	1	ESI+: 562
799	1	ESI+: 562
800	1	FAB+: 744
801	19	ESI+: 688
802	1	ESI+: 667
803	19	ESI+: 611
804	44	ESI-: 634
805	3	ESI+: 703
56	56	ESI: 661
806	4	ESI+: 650
807	44	ESI+: 636
808	19	ESI+: 658
809	19	ESI+: 581

TABLE 298

810	1	ESI+: 671
811	1	ESI+: 671
812	1	ESI-: 718
813	P23	ESI-: 641
	1	
814	1	ESI+: 687
815	1	ESI+: 687
816	19	ESI+: 587
817	19	ESI+: 664
818	P23	ESI+: 744
	1	
819	1	ESI+: 667
820	19	ESI+: 611
821	19	ESI+: 688
822	P9	ESI+: 681
	1	
	4	
823	1	FAB+: 666
	44	
824	1	ESI+: 655
825	4	ESI+: 641
826	1	ESI+: 513
827	36	ESI+: 599
828	1	ESI+: 792

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TABLE 298-continued

829	1	ESI+: 715
58	58	ESI+: 672
830	1	ESI+: 526
831	1	ESI+: 526
832	19	ESI+: 702
833	19	ESI+: 702
834	1	ESI+: 556
835	P33	ESI-: 601
	1	
836	1	ESI+: 644
837	1	ESI+: 567
838	58	ESI+: 595
839	11	ESI+: 580
840	35	ESI+: 596
841	1	ESI-: 680
842	1	FAB+: 605
843	1	ESI+: 721

TABLE 299

844	1	ESI+: 643
845	19	ESI+: 664
846	19	ESI+: 587
847	P33	FAB+: 541
	1	
848	1	FAB+: 587
849	1	FAB+: 587
850	1	FAB+: 587
851	1	FAB+: 587
852	1	ESI+: 701
853	58	ESI+: 581
854	1	FAB+: 591
855	1	FAB+: 591
856	4	ESI+: 674
		NMR1: 1.00-2.30 (8H, m), 2.94 (3H, s), 3.58 (3H, s), 4.07 (1H, brs), 4.74 (1H, d, J = 11.0 Hz), 4.77 (1H, d, J = 11.0 Hz), 5.18 (1H, s), 6.36 (1H, d, J = 6.9 Hz), 6.88 (1H, d, J = 8.4 Hz), 7.08-7.11 (1H, m), 7.16 (1H, d, J = 2.0 Hz), 7.18 (1H, d, J = 2.0 Hz), 7.26 (2H, d, J = 8.0 Hz), 7.30 (2H, d, J = 8.0 Hz), 7.43-7.48 (2H, m), 7.64 (1H, d, J = 2.0 Hz) 7.93-7.96 (1H, m), 11.42 (1H, s), 12.34 (1H, brs)
857	1	FAB+: 616
858	1	ESI+: 627
859	19	ESI+: 571
860	1	ESI+: 540
861	1	ESI+: 513
862	1	ESI+: 545
863	1	ESI+: 564
864	1	ESI+: 589
865	1	ESI+: 537
866	1	ESI+: 532
867	1	ESI+: 505
868	1	ESI+: 616
869	1	ESI+: 548
870	1	ESI+: 574
871	1	FAB+: 564
872	1	FAB+: 532
873	1	ESI+: 542
874	1	ESI+: 573
875	1	ESI+: 608
876	21	ESI+: 598
877	1	FAB+: 728

TABLE 300

878	1	FAB+: 651
879	1	FAB+: 603
880	1	FAB+: 764
881	1	FAB+: 687
882	1	FAB+: 764
883	1	FAB+: 689
884	1	ESI+: 766
885	1	ESI+: 689
886	1	ESI+: 764

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TABLE 300-continued

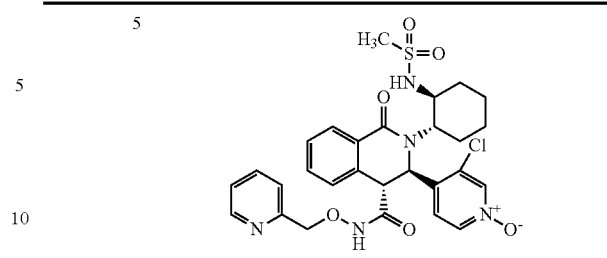
887	1	ESI+: 687
888	1	ESI-: 665
889	1	FAB+: 601
890	1	ESI+: 691
891	1	ESI+: 691
892	P9	ESI+: 678
	1	
893	1	ESI+: 714
894	1	FAB+: 637
895	1	FAB+: 758
896	1	ESI+: 758
897	1	FAB+: 636
898	P33	ESI+: 622
	1	
899	P33	APCI+: 435
	1	

TABLE 301

No	Structure
1	
2	
3	
4	

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TABLE 302

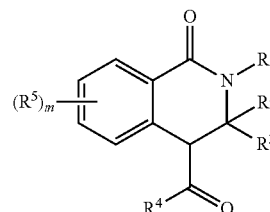


INDUSTRIAL APPLICABILITY

The compound (1) of the present invention as described above is useful as a therapeutic agent for the diseases in which BB2 receptors are related, in particular, for IBS since it has an excellent BB2 receptor antagonistic activity, and further, it exhibits excellent efficacy regarding bowel movement disorders.

The invention claimed is:

1. A method of antagonizing BB2 receptor in a patient suffering from irritable bowel syndrome, comprising administering to the patient in need thereof a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof:



in which groups R¹-R⁵ and m are as follows

R¹: lower alkylene-OH, lower alkylene-N(R⁶)(R⁶), lower alkylene-CO₂R⁰, cycloalkyl, cycloalkenyl, aryl, heterocyclic group, -(lower alkylene substituted with —OR⁰)-aryl or lower alkylene-heterocyclic group, wherein the lower alkylene, cycloalkyl, cycloalkenyl, aryl and heterocyclic group in R¹ may each be substituted,
R⁰: the same as or different from each other, each representing —H or lower alkyl,
R⁶: R⁰, —C(O)—R⁰, —CO₂-lower alkyl or —S(O)₂-lower alkyl,

R²: lower alkyl, lower alkylene-OR⁰, lower alkylene-aryl, lower alkylene-heterocyclic group, lower alkylene-N(R⁰)CO-aryl, lower alkylene-O-lower alkylene-aryl, —CO₂R⁰, —C(O)N(R²)₂, —C(O)N(R⁰)-aryl, —C(O)N(R⁰)-lower alkylene-aryl, or aryl, wherein the aryl and heterocyclic group in R² may each be substituted,

R³: —H or lower alkyl, or R² and R³ may be combined to form C₂₋₆ alkylene,

R⁴: —N(R⁷)(R⁸), —N(R⁰)-OH, —N(R¹⁰)-OR⁷, —N(R⁰)-N(R⁰)(R⁷), —N(R⁰)-S(O)₂-aryl, or —N(R⁰)-S(O)₂-R⁷, wherein the aryl in R⁴ may be substituted,

R⁷: lower alkyl, halogeno-lower alkyl, lower alkylene-CN, lower alkylene-OR⁰, lower alkylene-CO₂R⁰, lower alkylene-C(O)N(R⁰)₂, lower alkylene-C(O)N(R⁰)N(R⁰)₂, lower alkylene-C(=NH)NH₂, lower alkylene-C(=NOH)NH₂, heteroaryl, lower alkylene-X-aryl, or

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lower alkylene-X-heterocyclic group, wherein the lower alkylene, aryl, heteroaryl, and heterocyclic group in R⁷ may each be substituted,

X: single bond, —O—, —C(O)—, —N(R⁰)—, —S(O)_p—, or *—C(O)N(R⁰)—, wherein * in X represents a bond to lower alkylene,

m: an integer of 0 to 3,

p: an integer of 0 to 2,

R⁸: —H or lower alkyl, or R⁷ and R⁸ may be combined to form lower alkylene-N(R⁹)-lower alkylene, lower alkylene-CH(R⁹)-lower alkylene, lower alkylene-arylene-lower alkylene, or lower alkylene-arylene-C(O)—,

R⁹: aryl and heteroaryl which may each be substituted,

R¹⁰: H lower alkyl, or —C(O)R⁰,

R⁵: lower alkyl, halogeno-lower alkyl, halogen, nitro, —OR⁰, —O-halogeno-lower alkyl, —N(R⁰)₂, —O-lower alkylene-CO₂R⁰, or —O-lower alkylene-aryl, wherein the aryl in R⁵ may be substituted, provided that, when R⁴ is —N(R⁷)(R⁸),

(1) a compound wherein R¹ is unsubstituted cyclopentyl and R² is unsubstituted 2-thienyl;

(2) a compound wherein R¹ is unsubstituted cyclohexyl and R² is 4-methoxyphenyl;

(3) a compound wherein R¹ is 4-methoxyphenyl and R² is 4-methoxyphenyl; and

(4) a compound wherein R¹ is (morpholin-4-yl)ethyl and R² is 4-ethoxyphenyl are excluded, and

further provided that, 2,3-bis(4-chlorophenyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-(4-chlorobenzyl)-2-(4-chlorophenyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-2-cyclopropyl-N-(2-furylmethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-2-cyclopropyl-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

ethyl 3-[3-[3,5-bis(trifluoromethyl)phenyl]-4-[[2-(4-methoxyphenyl)ethyl]carbonyl]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]propanoate,

N-benzyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-oxo-2-(tetrahydrofuran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-N-(2-methoxyethyl)-2-(2-morpholin-4-ylethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

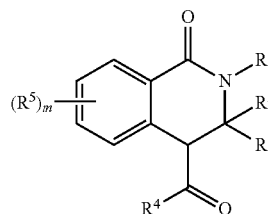
3-[3,5-bis(trifluoromethyl)phenyl]-2-(2-furylmethyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,

3-[3,5-bis(trifluoromethyl)phenyl]-N-(2-furylmethyl)-2-(2-morpholin-4-ylethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide, and

(4-chlorophenyl)[3-(4-chlorophenyl)-4-[(2-methoxyethyl)carbonyl]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]acetic acid are excluded.

2. A method of treating irritable bowel syndrome in a patient, comprising administering to the patient suffering from irritable bowel syndrome a compound represented by the formula (I) or a pharmaceutically acceptable salt thereof:

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in which groups R¹-R⁵ and m are as follows

R¹: lower alkylene-OH, lower alkylene-N(R⁰)(R⁶), lower alkylene-CO₂R⁰, cycloalkyl, cycloalkenyl, aryl, heterocyclic group, -(lower alkylene substituted with —OR⁰)-aryl or lower alkylene-heterocyclic group, wherein the lower alkylene, cycloalkyl, cycloalkenyl, aryl and heterocyclic group in R¹ may each be substituted,

R⁰: the same as or different from each other, each representing —H or lower alkyl,

R⁶: R⁰, —C(O)—R⁰, —CO₂-lower alkyl or —S(O)₂-lower alkyl,

R²: lower alkyl, lower alkylene-OR⁰, lower alkylene-aryl, lower alkylene-heterocyclic group, lower alkylene-N(R⁰)CO-aryl, lower alkylene-O-lower alkylene-aryl, —CO₂R⁰, —C(O)N(R⁰)₂, —C(O)N(R⁰)-aryl, —C(O)N(R⁰)-lower alkylene-aryl, or aryl, wherein the aryl and heterocyclic group in R² may each be substituted,

R³: —H or lower alkyl, or R² and R³ may be combined to form C₂₋₆ alkylene,

R⁴: —N(R⁷)(R⁸), —N(R⁰)—OH, —N(R¹⁰)—OR⁷, —N(R⁰)—N(R⁰)(R⁷), —N(R⁰)—S(O)₂-aryl, or —N(R⁰)—S(O)₂—R⁷, wherein the aryl in R⁴ may be substituted,

R⁷: lower alkyl, halogeno-lower alkyl, lower alkylene-CN, lower alkylene-OR⁰, lower alkylene-CO₂R⁰, lower alkylene-C(O)N(R⁰)₂, lower alkylene-C(O)N(R⁰)N(R⁰)₂, lower alkylene-C(=NH)NH₂, lower alkylene-C(=NOH)NH₂, heteroaryl, lower alkylene-X-aryl, or lower alkylene-X-heterocyclic group, wherein the lower alkylene, aryl, heteroaryl, and heterocyclic group in R⁷ may each be substituted,

X: single bond, —O—, —C(O)—, —N(R⁰)—, —S(O)_p—, or *—C(O)N(R⁰)—, wherein * in X represents a bond to lower alkylene,

m: an integer of 0 to 3,

p: an integer of 0 to 2,

R⁸: —H or lower alkyl, or R⁷ and R⁸ may be combined to form lower alkylene-N(R⁹)-lower alkylene, lower alkylene-CH(R⁹)-lower alkylene, lower alkylene-arylene-lower alkylene, or lower alkylene-arylene-C(O)—,

R⁹: aryl and heteroaryl which may each be substituted,

R¹⁰: —H, lower alkyl, or —C(O)R⁰,

R⁵: lower alkyl, halogeno-lower alkyl, halogen, nitro, —OR⁰, —O-halogeno-lower alkyl, —N(R⁰)₂, —O-lower alkylene-CO₂R⁰, or —O-lower alkylene-aryl, wherein the aryl in R⁵ may be substituted, provided that, when R⁴ is —N(R⁷)(R⁸),

(1) a compound wherein R¹ is unsubstituted cyclopentyl and R² is unsubstituted 2-thienyl;

(2) a compound wherein R¹ is unsubstituted cyclohexyl and R² is 4-methoxyphenyl;

(3) a compound wherein R¹ is 4-methoxyphenyl and R² is 4-methoxyphenyl; and

(4) a compound wherein R¹ is (morpholin-4-yl)ethyl and R² is 4-ethoxyphenyl are excluded, and

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further provided that, 2,3-bis(4-chlorophenyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 3-(4-chlorobenzyl)-2-(4-chlorophenyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 3-[3,5-bis(trifluoromethyl)phenyl]-2-cyclopropyl-N-(2-furylmethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 3-[3,5-bis(trifluoromethyl)phenyl]-2-cyclopropyl-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 ethyl 3-[3,5-bis(trifluoromethyl)phenyl]-4-[[2-(4-methoxyphenyl)ethyl]carbamoyl]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl}propanoate,
 N-benzyl-3-[3,5-bis(trifluoromethyl)phenyl]-1-oxo-2-(tetrahydrofuran-2-ylmethyl)-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 3-[3,5-bis(trifluoromethyl)phenyl]-N-(2-methoxyethyl)-2-(2-morpholin-4-ylethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 3-[3,5-bis(trifluoromethyl)phenyl]-2-(2-furylmethyl)-N-(2-methoxyethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide,
 3-[3,5-bis(trifluoromethyl)phenyl]-N-(2-furylmethyl)-2-(2-morpholin-4-ylethyl)-1-oxo-1,2,3,4-tetrahydroisoquinoline-4-carboxamide, and

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(4-chlorophenyl)[3-(4-chlorophenyl)-4-[(2-methoxyethyl)carbamoyl]-1-oxo-3,4-dihydroisoquinolin-2(1H)-yl]acetic acid are excluded.

3. The method as described in claim 2, wherein R³ is —H.

5 4. The method as described in claim 3, wherein R² is phenyl which may be substituted with halogen, lower alkyl, or —OR⁰.

5. The method as described in claim 4 or a pharmaceutically acceptable salt thereof, wherein R⁴ is —N(R⁰)-lower alkylene-(aryl or heteroaryl, which may each be substituted), or —N(R⁰)—O-lower alkylene-(aryl or heteroaryl, which may each be substituted).

6. The method as described in claim 5, wherein R¹ is (lower alkylene)-OH or substituted cycloalkyl {wherein said lower alkylene may be substituted with a member selected from the group consisting of —OH and phenyl (which may be substituted with halogen, lower alkyl, or —OR⁰), and said substituted cycloalkyl is substituted with a member selected from the group consisting of —OR⁰, —N(R⁰)₂, —N(R⁰)C(O)R⁰, —N(R⁰)-lower alkylene-OR⁰, —N(R⁰)S(O)₂-lower alkyl and heterocyclic group}.

7. The method according to claim 2, wherein the compound is (4-{{[(3R,4R)-3-(2,4-dichlorophenyl)-2-{{(1S,2S)-2-[(methylsulfonyl)amino]cyclohexyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-4-yl]carbonyl}amino]oxy[methyl]phenyl}acetic acid, or a pharmaceutically acceptable salt thereof.

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